EXHIBIT “A”

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF PUERTO RICO

GERARDO CAMPOS, ET AL.,	:	
Plaintiffs,	:	CASE NO. 3:12-cv-01529-ADC-BJM
v.	:	
SAFETY-KLEEN SYSTEMS, INC., ET AL.,	:	
Defendants.	:	

DECLARATION OF DR. PETER G. SHIELDS

Comes now, Peter G. Shields, M.D, who, pursuant to 28 U.S.C.A. § 1746 declares the following to be true subject to the penalty of perjury:

I have only been retained to evaluate the relationship between benzene exposures and CML in two cases that I can recall or have records for. The first time was in 2006, in a case captioned *Christopher v. Consolidated Rail Corporation.* I was retained to evaluate whether a plaintiff's work-related exposure to benzene caused his CML. As with the present case, I conducted a comprehensive review of the relevant epidemiological literature. I applied the Bradford Hill guidelines to evaluate causation. After my review, I determined that there was insufficient evidence that benzene causes a measureable increase in CML, at any dose. I issued a report in that case on August 24, 2006. A true and correct copy of that report is attached hereto as Exhibit 1. I did not provide oral testimony in that case. The instant case is only the second time that I have been retained in a benzene exposure and CML case. A true and correct copy of my report from this case is attached hereto as Exhibit 2.

I presume that I have only been retained in two cases involving benzene exposures and CML because there is insufficient evidence of causation. At no point in time has there been sufficient evidence that exposures to benzene at any level are capable of causing CML.

In 2008, I made a statement at a deposition that benzene exposure can cause chronic myelogenous leukemia ("CML"). At this time, I cannot recall the context for my response, but I have since reviewed the entire deposition and confirmed that it contained no other mention of CML or discussion of benzene and CML, besides the reference cited by Plaintiffs at page 39:5-21. The case in which I gave that testimony had nothing to do with CML, I was not designated to discuss CML, nor had I undertaken an evaluation of the literature specific to benzene exposure and CML in preparation for that deposition. The party who retained me did not benefit by my statement related to CML, and it was entirely unrelated to my testimony and opinions in that case. I was not asked about CML in the deposition or during the two days that I gave trial testimony for that case. I believe that if counsel had asked, I would have realized the error of my statement and corrected it at the time.

Since my 2006 report, there have been a number of publications that further support my opinions in this case that there is insufficient data to conclude that benzene causes CML. For this case, I undertook an evaluation of the literature on benzene exposure and CML as of 2014, as explained in my February 28, 2014 report and May 9, 2014 deposition. In fact, this relationship was recently considered by the International Agency for Research on Cancer, in 2009 with the full report in 2012, who considered CML and did not even provide a conclusion for limited evidence [1]. Several research studies specifically about CML risk factors that have recently been published cover large groups of workers and varied study designs, strengthening my opinions. These include a review article and meta-analysis of 15 separate studies [2]. The authors

wrote: "The meta-analysis indicated consistently a lack of association between benzene exposure and the risk of CML." Separately, a large population-based study published in 2009 using a huge registry of more than 15 million people failed to find associations for occupations that might involve benzene exposure and CML [3]. In a separate European very large prospective study, published in 2013, Saberi and colleagues considered benzene exposure specifically and CML risk, and found the results to be not statistically elevated [4]. For a different type of study, several publications from a large pooled analysis of refinery workers, some of whom have very large exposures, also did not find an increased risk of CML [5;6]. The authors wrote: "Conclusions: No convincing association was identified between MPD or CML and low exposure to benzene. The greater risk for exposures experienced in the 20 years before diagnosis needs investigating in more powerful studies with a wider range of exposure to benzene, and the biological plausibility further examined from a mechanistic viewpoint." These studies were published in 2012 and 2014, respectively. Also, a separate 2012 meta-analysis done by researchers at the National Cancer Institute failed to find a statistical association between benzene exposure and CML considering many types of occupations [7]. The strengths and limitations of the above studies have been discussed in my report.

I have reviewed the motions by Plaintiffs and these do not alter my opinions, nor do they represent my opinions accurately. The above research studies and opinions by various agencies show that as of today, benzene cannot be considered a cause of CML.

I declare under the penalty of perjury that the foregoing is true and correct.

Dr. Peter G. Shields Dated: July 15, 2014

Reference List

1. International Agency for Research On Cancer. Chemical Agents and Related Occupations: A Review of Human Carcinogens 100F. (100F). 2012. Lyon, France, World Health Organization. Ref Type: Serial (Book,Monograph)

2. Khalade,A., Jaakkola,M.S., Pukkala,E., and Jaakkola,J.J. (2010) Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environ.Health*, **9**, 31.

3. Pukkala,E., Martinsen,J.I., Lynge,E., Gunnarsdottir,H.K., Sparen,P., Tryggvadottir,L., Weiderpass,E., and Kjaerheim,K. (2009) Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol.*, **48**, 646-790.

4. Saberi,H.F., Christopher,Y., Peeters,P., Romieu,I., Xun,W., Riboli,E., Raaschou-Nielsen,O., Tjonneland,A., Becker,N., Nieters,A., Trichopoulou,A., Bamia,C., Orfanos,P., Oddone,E., Lujan-Barroso,L., Dorronsoro,M., Navarro,C., Barricarte,A., Molina-Montes,E., Wareham,N., Vineis,P., and Vermeulen,R. (2013) Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Occup Environ.Med.*, **70**, 464-470.

5. Schnatter,A.R., Glass,D.C., Tang,G., Irons,R.D., and Rushton,L. (2012) Myelodysplastic Syndrome and Benzene Exposure Among Petroleum Workers: An International Pooled Analysis. *J.Natl.Cancer Inst.*.

6. Glass,D.C., Schnatter,A.R., Tang,G., Irons,R.D., and Rushton,L. (2014) Risk of myeloproliferative disease and chronic myeloid leukaemia following exposure to low-level benzene in a nested case-control study of petroleum workers. *Occup Environ.Med.*, **71**, 266-274.

7. Vlaanderen,J., Lan,Q., Kromhout,H., Rothman,N., and Vermeulen,R. (2012) Occupational benzene exposure and the risk of chronic myeloid leukemia: a meta-analysis of cohort studies incorporating study quality dimensions. *Am.J Ind.Med.*, **55**, 779-785.

EXHIBIT 1

GEORGETOWN UNIVERSITY MEDICAL CENTER
LOMBARDI COMPREHENSIVE CANCER CENTER
Research ! Education ! Treatment

Peter G. Shields, M.D.
Associate Director for Population Sciences
Director of Cancer Genetics and Epidemiology
Lombardi Comprehensive Cancer Center
Georgetown University School of Medicine
LL level, Room S-150, Box 571465
3800 Reservoir Rd., NW
Washington, DC 20057-1465

Tel: (202) 687-0003
Fax: (202) 687-0004
Pager: 800-309-8140
PGS2@GEORGETOWN.EDU

August 24, 2006

Kendra Smith, Esq.
Burns, White & Hickton
106 Isabella Street
Four Northshore Center
Pittsburgh, PA 15212

Re: Christopher v. Consolidated Rail Corporation

Dear Ms. Smith:

This report will serve to provide my opinions regarding the above cited case. I have been provided with legal documents for the Complaint (undated), Answers to Interrogatories (undated), Christopher deposition (April 6, 2006), and Christopher video deposition (April 13, 2006). The medical records reviewed were from the University Hospitals of Cleveland, Dr. Barry Effron, St. Jude Medical Center, Ireland Cancer Center, railroad employment records, Lake West Hospital, Hillcrest Hospital, and Dr. Martha Hackett. I also have reviewed the reports of Drs. Richard Lipsey (June 9, 2006), Bernard Goldstein (June 12, 2006), and Arthur Frank (February 20, 2006). If there are further data or materials of any sort provided to me, other materials or other relevant information after the date of this report, then my opinions, or the scope of my opinions, may be revised. The opinions expressed herein are my own, and were not developed in relationship to my Georgetown University service.

A list of cited references appear at the end of this report. Attached is my Curriculum Vitae and list of prior testimony.

SCOPE OF OPINIONS AND LEGAL DOCUMENTS

Mr. Christopher has been diagnosed in 2005 with a Philadelphia chromosome-positive chronic myelogenous leukemia (CML) and is in cytogenetic remission at last report this past

spring. He had worked for the railroad as a sheet-metal and pipefitter mechanic for about 21 years and he is claiming that his work has caused his leukemia. For the purposes of this report, I have been asked to focus on the claimed exposure to benzene from pure benzene and benzene-containing products as the cause of his CML. In this case, there is no quantitative documentation of potential benzene exposure, either by airborne levels or personal monitoring.

The complaint stated:

> "In the performance of his duties, Plaintiff used and/or worked around others who used and/or hauled toxic and ultrahazardous products and substances including, but not limited to asbestos products and/or silica and/or coal and/or benzene and or other toxic and hazardous or ultrahazardous materials and substances on railroad cars, locomotives, locomotive boilers and their appurtenances, and Plaintiff was exposed to the inhalation of and or exposure to toxic and or hazardous or ultra hazardous materials including but not limited to asbestos dust and/or fibers, and or silica sand and/or silica dust, and/or coal and/or coal dust and/or benzene and or other toxic and hazardous or ultrahazardous materials and substances, resulting from the hauling and/or use of these products and/or materials."

QUALIFICATIONS

As my Curriculum Vitae will provide in more detail, I am currently a Professor in the Departments of Oncology and Medicine at the Georgetown University School of Medicine. I also am a Professor in the Department of Pediatrics and Child Health at the Howard University School of Medicine. In the Department of Oncology at Georgetown, I am the vice-Chair of the Department and Chief of the Division of Cancer Genetics and Epidemiology. I also am the Associate Director for Cancer Control and Population Sciences in the Lombardi Comprehensive Cancer Center at the Georgetown University Medical Center, and the Program Leader for the Cancer Genetics and Epidemiology Program. As such, I am responsible for directing a multidisciplinary research program that focuses on identifying the environmental and genetic causes of cancer using epidemiology and biomarkers. Through this, I am responsible for mentoring many junior (and sometimes senior) faculty, postdoctoral fellows, Ph.D. and masters graduate students, and undergraduate students. My teaching responsibilities include giving lectures and serving as a course director in the areas of cancer risk and epidemiology. Regularly, I am an invited speaker at national and international meetings, and at universities around the world. Prior to my position at the Lombardi Comprehensive Cancer Center, I was a tenured investigator and Chief of the Molecular Epidemiology Section of the Laboratory of Human Carcinogenesis at the National Cancer Institute. Throughout my career, I have conducted research into the environmental and genetic causes of cancer, as well as the development of tests for cancer risk and early detection of cancer. Relevant to this case, I am an expert in the

development of cancer, which include leukemias, and have published widely. My publications have appeared in highly respected peer-reviewed journals (including those that focus on the occupational setting). Also relevant to this case is that my work is considered toxicological in nature, because of the consideration of how carcinogens or cancer therapies affect the body, and I frequently use laboratory methods (including animal studies). I am, or have been, on the editorial board of several journals; many other journals rely on my opinions as a peer-reviewer. I also sit on various committees and panels that provide research opinions, identify funding priorities or review other investigators' research proposals about the causes of cancer, including those relevant to this case. As further evidence of the respect from my peers, I had been elected by them to lead scientific groups of epidemiologists. Recently, I have been appointed to the Executive Committee of a professional association dedicated to the prevention of cancer. Lastly, I remain clinically active, caring for hematology and oncology patients, including CML. My clinical expertise has been recognized as I have been twice appointed to the District of Columbia Board of Medicine. Thus, I consider myself an expert in cancer risk, cancer and leukemia causation, carcinogenesis, epidemiology, and hematology/oncology.

MEDICAL RECORD REVIEW

Mr. Christopher was born on October 26, 1938. He is currently a 67 year old Caucasian male.

Mr. Christopher had a hernia repair and arthroscopic surgery of the knee in 1980. The knee injury occurred from work. He also reported having eye injuries from welding flashes. At deposition, he also had a back injury that resulted in surgery. For the knee, hernia and back surgery, he was off from work for about 5 months.

Mr. Christopher was diagnosed with paroxysmal atrial fibrillation and syncope in the early 1990s. A tilt table test was done for syncope and was positive for hypotension and asystole on November 4, 1992. The report stated that this was consistent with a neurally-mediated syncope. There were several admissions to the hospital for the atrial fibrillation, which would produce dizziness and weakness. He was treated with a variety of heart medications and coumadin. Mr. Christopher went out on permanent disability in 1993 due to this heart condition. He was told that he could not work because of his coumadin treatment. In October, 1992, his total white blood cell count (WBC) was 5.2.

In 1993, Mr. Christopher was arrested for drug trafficking. He went to prison and also underwent drug rehabilitation.

In 2000 and 2001, Mr. Christopher underwent a radio-ablation and was treated with anti-arrhythmic therapy for his atrial fibrillation. A CAT scan of the abdomen on July 26, 2000 showed a normal size spleen. In September, 2001, he had a left inguinal hernia repair. There was an admission to Lake West Hospital on July 17, 2002 for vomiting and weakness. A noncontrast CAT scan of the brain was normal. His blood counts were normal.

In November, 2003, Mr. Christopher went to the hospital for shortness of breath. His

blood counts were normal. He had a pleural effusion, thought to be related to his prior surgical procedures. A thoracentesis was done as an outpatient under sonogram-guidance and 120 cc of fluid was removed. The cytology was negative. Pulmonary function tests showed an FEV1 of 73%, his FEV1/FVC ratio was 69% and his FVC was 84% of predicted. A CAT scan showed an occluded left pulmonary vein. The WBC was 8.0.

On January 15, 2004, Mr. Christopher underwent repair of an abdominal aortic aneurysm. This was done without complications. The pathology report indicated atherosclerotic plaques. His WBC at the time was 5.7.

The WBC on June 4, 2004 was 4.77, with a normal differential count.

A chest x-ray from November 11, 2004 was reported as having evidence of COPD, with biapical pleural and parenchymal scarring, hyperinflation of the lungs, prominence of the central pulmonary arteries, but no effusions.

Mr. Christopher had a CAT scan of the chest on January 21, 2005. The occluded left pulmonary vein was unchanged. Apical bullae were seen, reported to be consistent with emphysema. No parenchymal disease or pleural plaques were reported. The spleen was not enlarged.

Mr. Christopher was admitted to the hospital on September 7, 2005 for an elevated WBC of 59,000, with 69% neutrophils and metamyelocytes, but no blasts. The elevated WBC count was found incidentally during a pre-operative work-up for eye surgery. His past medical history was listed as hypertension, glaucoma, and atrial fibrillation, and he had a surgical history of a pacemaker placement and abdominal aortic aneurysm repair. He was being treated with coumadin, digoxin, Lovastatin, Lasix and Atenenol. He was relatively asymptomatic, except for some fatigue. He had chronic complaints of exertional shortness of breath that predated any abnormal blood counts. His platelets were normal at 199,000 and he was not anemic. A bone marrow showed 90-95% cellularity with only 2% blasts. Chromosomal analysis indicated that all 20 metaphases contained the t(9;22)(q34;qll.2) translocation as the sole detectable chromosomal change. Flow cytometry was consistent with CML, and the cytogenetics showed the 9,22 translocation. FISH analysis also was done. The diagnosis was CML in chronic phase. An enlarged spleen was not felt. He was started on Gleevec at 400 mg per day.

On October 20, 2005, Mr. Christopher was evaluated at the Ireland Cancer Center by Dr. Deepjot Singh. His WBC, while on Gleevec was 10.1. The hematocrit and platelet count were normal.

The pacemaker was exchanged on December 12, 2005.

Mr. Christopher had a skin biopsy of a rash on December 6, 2005. The pathology diagnosis was drug eruption.

At the beginning of 2006, it was reported that Mr. Christopher had severe glaucoma, optic nerve glaucoma-related damage and corneal decompensation. It was stated that his rash was thought secondary to Gleevec, and he was treated with a steroid injection and creams.

FISH analysis on January 5, 2006, was negative for the BCR/ABL translocation, indicating a remission.

The last record about his CML was on March 9, 2006, and it was reported that he

remained in remission. He was still on Gleevec at 400 mg. The WBC was 8.4, and he had a mild anemia with an hematocrit of 34%. It was reported that based on a blood test one month earlier, that he was in cytogenetic remission. It was stated that his rash, thought to be secondary to Gleevec, had resolved.

The Answers to Interrogatories stated that due to the CML, Mr. Christopher suffers headaches, upset stomach, fatigue, depression, mouth sores, hives and peeling of the hands and feet as a medication reaction. At deposition, he stated he broke out in hives and his hands and feet would peel. He did not know if these things were linked to Gleevec or CML. In April, 2006, Mr. Christopher stated at deposition that he does not have symptoms related to the CML, although this was later clarified to say that he had fatigue and tingling on the tongue.

Family history: As of 2005, Mr. Christopher had a brother who died with cardiovascular disease according to the medical records and unknown causes according to the deposition testimony. He died at the age of 80. He had a sister with lung cancer who died at the age of 60, who was a nonsmoker. He also had a sister with breast cancer. His father died of heart failure and hardening of the arteries. His mother died at the age of 62 from a cerebral hemorrhage.

Social history: Mr. Christopher stated in the Interrogatories that he smoked 1-2 packs per day from 1956 to 1990, using different brands. In 2005, it was reported that Mr. Christopher occasionally used alcohol, and was a 2 pack per day smoker for 20 years, but had quit around 1990. At deposition, he stated he began to smoke at the age of 18 until the age of 50. He said he smoked 1-2 packs per day.

In, March, 2006, Mr. Christopher weighed 175 pounds. For the Answers to Interrogatories, it was stated that Mr. Christopher was 5' ,10.5" and weighed 185 pounds.

During Mr. Christopher's first marriage, his wife smoked about a pack per day. He was married from 1960 to 1975. His father smoked little cigars regularly and occasionally cigarettes.

Occupational and exposure history: The complaint stated that Mr. Christopher worked from 1959 to 1993 as a pipefitter. He went out on disability in 1993 due to his heart condition and treatment with anticoagulants. He was a member of the Sheet Metal Workers union. Prior to that, he worked as a parts handler, where he brought parts to lathes at a plant that made impeller blades for jet engines. His work title was called a trucker. He also worked for a year as a laborer for a company that laid gas and telephone lines, as a traffic flagger. It also was stated that he worked for about a year doing road work surveys as a surveyor assistant. At deposition, Mr. Christopher stated that he occasionally had second jobs while working for the railroad, for example selling clothes, bartending and working in a bowling alley. Following the railroad work and retirement, Mr. Christopher worked as a bartender.

Mr. Christopher testified that he did not have any unusual hobbies or home activities.

Regarding his railroad employment, it was written in the Answers that: "I began work for the New York Central Railroad in September of 1959 at the Colllinwood backstop. In 1968 the New York Central merged with the Pennsylvania Railroad to become Penn Central Railroad.

The Penn Central Railroad was merged into Conrail in 1976. The Collinwood backshop closed in 1980 and I then worked In the same yard at the diesel terminal my retirement in 1993."

Mr. Christopher also wrote in his Answers:

> " My most significant exposures to asbestos and benzene were while working in the Collinwood backshop for the New York Central/Penn Central/Conrail Railroad from 1959 until the backshop closed in 1980. I hired in at the railroad in 1959 and worked for two years in the Collinwood backshop as a sheet metal worker/pipe fitter apprentice. I was then promoted to sheet metal worker/pipe fitter mechanic, which I remained until my retirement in 1993.
>
> The backshop did heavy repairs, primarily on diesel locomotives, which involved taking the locomotives completely apart, refurbishing the parts, and reassembling them.
>
> As an apprentice I worked in all of the departments in the backshop as a learning experience. As a mechanic, based on seniority, I would bid into jobs in the various departments as they became available.
>
> One way I was exposed to asbestos was in rebuilding the steam generators which supplied the heat in passenger cars. Each generator had coils, which were encased in asbestos cement. Working side by side, boilermakers would chip out the old asbestos cement and remove the coils. This generated clouds of dust. Then the sheet metal workers would reinstall the coils, mixing new batches of asbestos cement by dumping bags of asbestos cement into tubs (kicking up lots of dust) and then adding water. I personally did this job many times.
>
> Dismantling diesel locomotives involved freeing up over 100 pipes, many of which were covered with asbestos pipe covering. Removing the pipes and the pipe covering generated dust. I also then had to remove the gaskets from the pipe flanges, by grinding, or hammering and chiseling: or wire brushing, or with a welding torch. Removing gaskets also generated significant dust.
>
> Over the years in the Collinwood yards many of the old buildings were torn down and the dust from the demolition would blow around our workspaces.
>
> In the backshop benzene solvents were used to clean oil engine parts, to prevent rust. The dismantled oil engine parts were put into 8' x 10' wire baskets, which were then lowered into agitating vats filled with the benzene solvent. The benzene solvent came in metal drums. Either the laborers or the mechanics would empty the drums into the vats, and after the solvent was too dirty to use, it was drained to floor drains, and the laborers or mechanics would wash the vats with water and steam hoses. We also sometimes cleaned our tools and washed our hands in the benzene agitating vats."

At deposition, Mr. Christopher said that he worked around "harmful substances", specifically, "asbestos, pure muriatic acid, hydrochloric acid, carbon tet" and other chemicals that end in "lene" or "tween".

At deposition, Mr. Christopher testified that he first worked as a sheet metal worker apprentice for three-four years. This required him to work 6 months in different departments. His work was all indoors about 75% of the time. During this time, he learned how to weld and build engines. He worked on diesel engines, rather than steam engines. At that time, parts were washed in vats containing lye. He also reported that the internal parts were washed in benzene or different kinds of solvents. He would use a wire brush to remove grease. In the steam generator department, there were 2 or 3 vats that were 2 - 4 feet in size. He said he knew it was benzene because of the sweet smell. He claimed that in some vats it was pure benzene or cleaning solvents that were benzene-derivatives. He did not recall the names, but said that they ended in "l-e-n-e-", perhaps xylene, toluene or trichloroethylene. He stated that sometimes it was his job to empty the vats, for example if he had to repair the pipes, although there were laborers would do the routine maintenance. He stated that the solvent would just be emptied on the floor, and the solvent would go down a drain. When he was done, he would refill the tanks.

Next, Mr. Christopher was a step-up sheet metal and pipe fitter mechanic in the backshop. The backshop closed in 1980. He would do similar work as the above, but bigger jobs. More often, he would do rebuilding, rather than stripping engines, so that the parts were already cleaned. He worked in different departments. His job duties did not change for many years, even through mergers. He worked in the specialty shops more than the diesel shop. Early, he worked in a roundhouse hooking up locomotives. Mr. Christopher also claimed that benzene was in cleaning materials. And that guys would wash their hands with benzene and with cleaning agents that contained benzene. It was reported by him that he used benzene most of the time, which would come in 15-55 gallon drums. He stated that he knew it was benzene by the smell, and that some barrels were labeled as benzene. He also claimed that he was around benzene about 50% of the time from 1962 to 1980.

From 1980 to 1993, he worked in a diesel shop doing minor repairs. He claimed that he also used benzene cleaning parts. He also claimed he was around benzene 50% of the time, although the Answers stated that most of his exposure was prior to 1980.

Mr. Christopher testified that he never wore a respirator, although he wore gloves at different times.

CHRONIC MYELOGENOUS LEUKEMIA

Mr. Christopher has CML, which is a type of chronic leukemia. He presented with typical findings, namely an elevated white blood cell count without symptoms or other blood abnormalities. The molecular and cytogenetic work-up confirmed the diagnosis of CML. Mr. Christopher has a 9,22 translocation, and in the clinically setting of a chronic leukemia, is diagnostic for CML. Mr. Christopher received the diagnosis of the CML from his treating physicians, and I concur with this diagnosis, although I have not reviewed the actual pathology slides.

Leukemias are one type of many hematological malignancies. All of these are clonal

disorders that are composed of a single and specific cell type. As with other types of cancers, the cells of these clonal stem cell disorders fail to differentiate and reproduce uncontrollably, crowding out space for normal bone marrow elements. Actually, leukemias also are a heterogeneous group of blood cell malignancies. They are classified as acute or chronic, and originate from either myeloid or lymphoid lineages The diagnosis of leukemia is made by examining the bone marrow with a microscope, flow cytometry, immunohistochemisty and chromosomal analysis. Among the reasons why it is important to identify the type of leukemia is that the biology, treatment and prognosis can be very different.

CML also is classified as a myeloproliferative disorder, but is very different from other myeloproliferative disorders because of its Philadelphia chromosome positivity [1-4]. All of these also have very different clinical histories and treatments, although there may be some overlap as one develops overtime.

CML is an uncommon disorder, accounting for about 4,800 new cases in the US in 2005 [5]. This is among a total of 34,810 new cases of all leukemia and is less than half as common as AML with about 11,910 cases per year. The annual incidence of CML is 1.6 cases per 100,000 adults [5].

CML clinically has three phases, namely the chronic phase, the accelerated phase and the blast phase. Mr. Christopher is currently in the chronic phase. CML is diagnosed by the clinical history and the finding of the Philadelphia chromosome [2-4]. Patients typically present in the chronic phase, without symptoms, and the disease is detected by a routine blood test [6]. Eventually, patients may complain of weakness, weight loss and discomfort due to a large spleen. The criteria for blast phase include a blast count in the bone marrow greater than 20-30%, depending on the criteria. These are often attributed to rising WBC and consequent anemia.

The Philadelphia chromosome is a reciprocal translocation from chromosome 9 to chromosome 22 that involves the *ABL1* gene on chromosome 9 and the *BCR* (break point cluster) gene on chromosome 22 [4;6]. This is termed the *BCR-ABL* translocation. The resultant gene fusion makes a protein that has tyrosine kinase activity. This protein leads to deregulated cellular proliferation, cells that are less able to adhere to the bone marrow and decreased program cell death in response to mutagens.

Sometimes, other cytogenetic abnormalities are seen in CML, such as trisomy 8, isochromosome 17 and a duplicate Philadelphia chromosome [6], but these are not the type associated with leukemias thought to be caused by chemotherapy or benzene [4]. Specifically, chromosome 7 deletion occurs in less than 5% of CML cases and chromosome 5 deletions rare [7]. A search for reported cases in the National Cancer Institute CGAP database shows that there are only 27 cases are found in that database for -5 deletions and 112 cases for -7 deletions (http://cgap.nci.nih.gov/Chromosomes/Mitelman). (It is common that as CML progresses to blast phase and chromosome 7 deletions can be observed there, but -5 are still uncommon [8].)

There are several available treatments for CML. Without treatment, patients with chronic phase CML will progress to the other phases in 3 - 5 years [6]. The risk for transformation is about 3 - 4% per year [9]. CML in blast phase is highly refractory to chemotherapy and so is rapidly fatal. The latest treatment for CML takes advantage of the molecular changes caused by

the *BCR-ABL* translocation and its tyrosine kinase activity [4;6]. Gleevec (imatinib mesylate) is a selective tyrosine kinase activity inhibitor and a very successful treatment for CML. It almost always leads to a complete cytogenetic response, about 96% of the time, where Philadelphia chromosome positive cells are no longer detected. While there have been earlier proposed prognostic factors for CML, such as those proposed by Sokol [6;9], these are no longer clearly valid since the development of Gleevec. The common side effects of Gleevec include nausea, diarrhea, fluid retention (including periorbital edema), bone pain and muscle cramping. Elevation in liver enzymes and dermatologic reactions are less common. Recently, quantitative PCR for the transcription product has shown the best responses are those for persons with a 3 log decrease in transcript over 12 months [10]. The clinical trials for Gleevec only started in 1998, so that the maximum follow-up time for patients is only since then, about 4 years [10]. The survival estimate is 96% at 3 years and 82% at 4 years [10;11]. The longest responders were those with complete cytogenetic remission, as with Mr. Christopher. Gleevec, at higher doses, also has activity in persons with accelerated phase (55%), and somewhat in blast phase (18%), at 36 months. It is estimated that Gleevec, compared to older treatments such as interferon, improves incremental 10 year survival by 25% and saves about $43,000 per year of life [12]. Second generation tyrosine kinase inhibitors, or drugs for downstream molecular targets currently in clinical trials, for example, desatinib, are showing good success.

The only curative treatment for CML is stem cell or bone marrow transplantation [10]. But, it has been recently projected that long term survival for Gleevec is better than bone marrow or stem cell transplantation, which was previously the best long term option for CML [13]. Transplantation from siblings yields a 60% five year survival, and about 50% for unrelated donors. This would now be used for persons who become refractory to Gleevec and clinical trials are exhausted for newer drugs. It also is used for blast phase, and in some persons in accelerated phase who also are refractory to non-transplant treatments. It is expected that transplantation will be needed even less often, and the CML will become a very long term chronic disease.

CML is more common in men than in women, and the median age at diagnosis is 65 years old [6]. It also is more common in African Americans than in Whites. The causes of CML is essentially unknown, although there are some associations with radiation . For example, increase risk has been reported for atomic bomb survivors, radiologists and in persons treated with radiation therapy [6;14-17]. Being overweight may also be a risk factor for CML [18] and for leukemia without specification to cell type [19].

There is some evidence for increased risk for CML from cigarette smoking [20-22], but other studies are null [18;23]. A dose-response relationship and risks of about 1.4 were reported for former smokers [21]. Some notable reviews include CML by inference [24;25]. There also is some evidence that smoking increases the progression to blast crisis [26]. There is good data to indicate that cigarette smoking is weakly associated with an acute myeloid leukemia and preleukemia. The reported risks are about 1.5-2.0-fold [22;27-34], and a dose-response effect has been reported [18;22;29;33;35;36]. For example, in a large cohort study of 248,000 United States veterans, an overall relative risk was reported at 1.53, and for persons smoking more than

21 cigarettes per day the risk was 1.93 (95% CI = 1.45 - 2.52) [22]. Some studies do not show an association [21;37;38], and many studies do not distinguish among the types of leukemia [36;39]. The cytogenetic abnormalities in AML are more typically chromosome 7 rather than chromosome 5 abnormalities for a cigarette smoking association [27]. The conclusion of a meta-analysis by Dr. Brownson indicated a pooled risk from many studies of 1.4 (95% CI = 1.2-1.6) for smoking and acute leukemia [40]. Other workers have similar conclusions [24;31;41]. It is unknown why smoking causes leukemia, but one hypothesis is that cigarette contains benzene, among other human carcinogens [42]. It has been estimated that the benzene component is responsible for between 10% and 50% of all leukemia deaths, and up to 60% of AML [43].

Secondary leukemias is a common term reflecting some pre-existing condition or exposure that then developed into leukemia. The application of this term is reserved for persons with prior history of myelodysplastic syndromes (MDS), or persons with prior exposures to cancer chemotherapy [44-46]. Among the secondary leukemias, about 60-70% are related to MDS, while the others are therapy related [45]. Some people analogize this to benzene-related leukemia in persons with high levels of benzene exposure, and so there is some consideration by plaintiff's experts of this in relation to claims that benzene can cause CML, as an analogy to AML. Secondary leukemias occur following some chemotherapy or radiotherapy treatments, such as for Hodgkins lymphoma and breast cancer [45;47-49]. About 7%-15% of AML can be considered as secondary [45;50]; there is no particular histological subtype more common for secondary leukemias (except for secondary leukemias from topoisomerase II inhibitors that are usually M4 or M5) [44]. These treatments exemplify target organ specificity, because they only cause acute leukemia and not other types of leukemia or cancer. The secondary leukemias from chemotherapy often are accompanied by abnormal cytogenetics [45;51;52], which are not found in CML. The frequency of chromosomal abnormalities of some type range from 68-96% in therapy-related AML, but the distribution differs from *de novo* AML by more often having 11q23 and complex karyotypes (more than one abnormality) [51] , and -5 and -7 abnormalities [44]. In *de novo* leukemias, the incidence of -5 and -7 abnormalities are 2% and 4%, respectively [53]. Among the acute leukemias that are therapy-related, this is about 10% for either a -5 or -7 deletion (about 5% have it alone and 5% have it as a complex karyotype) [45;50;54]. The -7 abnormality is more common than the -5 abnormality, about 5% for the former and 2% for the latter [55].

Importantly, I am not aware of scientific studies that indicate that either the chromosome -5 or -7 abnormalities are common in CML (see above). Conversely, the 9,22 translocation characteristic for CML is rarely seen in cases of AML, occurring in less than 1% of adult AML [56-58], and these may be persons with previously undetected CML. (The 9,22 translocation is more commonly seen in acute lymphocytic leukemia [58].) It also is important to note that CML is not considered a leukemia secondary to chemotherapy, and that 9,22 translocations are rare [47;59]. For example, it has been reported that the 9,22 translocation occurs in cases of secondary leukemia from topoisomerase II inhibitors, but this is uncommon [59;60]. There is essentially about 25 cases in the world's literature [59;61]. Because it is uncommon, it is unclear if these really are secondary leukemias, or a *de novo* CML.

Acute leukemia secondary to benzene has been considered to follow a similar mechanism as other secondary leukemias from alkylating agents, because the same chromosomal abnormalities can be found (although not in all studies)[62;63], and so is sometimes more broadly referred to as a secondary leukemia [45-47]. The 9,22 Philadelphia chromosome was not reported in these studies. I am aware of one study that reported several cases with the Philadelphia chromosome, but these were mostly in people with prior CML, and there was no relationship with benzene exposure [62].

METHODOLOGICAL APPROACHES TO INDIVIDUAL RISK ASSESSMENT

There are well-established practices for considering if a chemical can cause cancer. Typical of other physicians and scientists, my initial approach before considering the individual's situation and alleged exposures is to assess if there is a relationship of the alleged exposure to the identified cancer, at any level of exposure. This is done by reviewing scientific textbooks and articles, doing computerized literature searches and drawing upon my experience as a researcher, clinician and epidemiologist. The method for determination of cancer causality is described below. It is important to assess different types of scientific data, relying on the best studies, and even though a researcher might postulate causality (e.g., as might be done through a publication of a case report, or a case series), this is different from concluding a causal relationship of exposure to an outcome. Among the types of data that might be useful, human epidemiological data is substantially more helpful than nonhuman data, assuming the epidemiological studies are of good quality. If there is sufficient epidemiological data to make a conclusion, then experimental animal or other studies are sometimes considered only in the context of understanding biological mechanisms. If there is sufficient reason to consider that the chemical has a potential to cause the type of cancer identified for the individual or a group of individuals (target organ specificity is important), then an assessment is made to determine the doses reported in the literature that may be associated with an increased cancer risk, and in what settings. The dose, i.e., how much of a carcinogen enters the body and then reaches the critical organs and targets within the organ, best determines an individual's cancer risk, as carcinogens clearly have a dose-response relationship. One must consider that exposure may not be a sufficient marker for dose. Importantly, there is some level below which we can no longer measure an increased risk, and so any conclusions of cancer causation for exposures below that level are speculative, unsupported, and at best only hypothetical. (Herein, the concept of increased risk is accompanied by the conventional use of statistics and findings of statistical significance.) A mechanistic understanding of the carcinogenic process (known or hypothesized) is considered in the context of the alleged exposure/dose and disease in the patient.

Assuming that there is sufficient reason to believe that there is some exposure/dose that might increase cancer risk because of available scientific data, then the degree and circumstances of the exposure from the literature is assessed in relation to the increased risk of the particular

cancer. This is then placed into the context of alleged and/or documented exposures in an individual or group of individuals, including latency. If the exposure level of the individual under consideration is less than that reported in the literature, or the route of exposure is different, then the chemical in question is less likely or unlikely to have caused cancer in the individual. Other unique circumstances are considered, such as a concurrent disease, comorbidities, and other risk factors (e.g., lifestyle, diet, work place, medication) that might make the individual more or less susceptible. And also if similar exposures occurred from different sources, and the relative contribution of each source is considered. Finally, the above information is integrated and a conclusion is made about the probability of causality in a person. A concurrent step for assessing causality in an individual is to confirm the diagnosis, as sometimes incorrect diagnoses are made, the pathology is not definitive or other diagnoses are likely and so would not be appropriately related to the alleged exposure in the individual. In this case, I have reviewed medical records, and considered the scientific literature in the context of the plaintiff's CML. I have not reviewed the pathology slides from the bone marrow examination or the peripheral blood smear. However, I have no reason to question the diagnosis of CML in Mr. Christopher.

Cancer causation: The evaluation of cancer causation, i.e., can an exposure cause cancer, requires examination of different types of data and studies. Published guidelines exist for assessing causality, such as those proposed by Sir Austin Bradford-Hill [64]. These guidelines, others [65-68], and my experience allow me to conceptually develop an opinion about causation. Actually, similar principles espoused by Sir Bradford-Hill were well-applied earlier in the first Surgeon General's Report on smoking and health, concluding in 1964 that smoking causes lung cancer in men [69]. It has been argued that the Bradford-Hill criteria may be difficult to apply or has limitations [65;70], but there is an appeal for having the best possible framework to guide research agendas and study design [66;67]. It also has been considered that stating the statistics is sufficient to communicate causality, although not considering the level of risk, or reporting such, is not informative [71]. Some of the different models for assessing causality reflect a purely scientific perspective and debate, while others are derived to satisfy public health needs. For the approach to litigation, however, rather than for debates among epidemiologists, the Bradford-Hill methodology is appropriate and useful.

While not all of Bradford-Hill criteria are required to be met, there are some criteria that if violated would exclude the likelihood of causation, while fulfilling some may not lead to a definitive conclusion of causation without considering other criteria. Among the most important criteria is consistency in the literature, that is, do several well-designed and well-conducted epidemiology studies lead to similar findings in different populations, using different study designs. It should be noted that no single epidemiological study is definitive, and the consideration of a scientific report is performed in the context of other published studies. As an example of consistency within the epidemiological literature, Table 1 shows selected studies of tobacco smoking. In this example, in virtually every study ever done on tobacco smokers, an increased lung cancer rate or risk is seen. A determination of a biological gradient also is important, i.e., do scientific publications show a dose-response relationship, and do those doses

Table 1
Selected Lung Cancer and Smoking Studies
Consistency of Association

Cohort	**Number of subjects**	**Positive lung cancer association?**
British Doctors [72]	34439	Yes
ACS-25 State Study [73;74]	120000 men 619925 women	Yes Yes
U.S. Veterans [75]	293,958	Yes
Japanese Study [76]	265000	Yes
ACS – 9 State Study [77]	187,783	Yes
Canadian Veterans [78]	78000	Yes
Swedish Study [78]	25,444	Yes
California Study [79]	68,153	Yes
MRFIT [80]	12,866	Yes
Iowa Women's Health Study [81]	41,843	Yes
Norwegian Study [82]	68,825	Yes

occur in the human exposure circumstance of interest. Another criteria is the strength of association, which allows one to consider if the reported association in an epidemiological study is plausible (e.g., not too high or too low). An evaluation of temporality considers if the exposure sufficiently preceded the cancer effect to allow for latency. Specificity considers if the cancer has other reported causes and if the effect occurs in the identified target organ. Given that lung cancer was a rare disease before smoking, lung cancer and tobacco smoking is an example of specificity. Coherence refers to an evaluation and agreement of different types of scientific data (epidemiological, laboratory animal studies, cell culture models, etc.), and do they provide similar findings that lead to a mechanistic understanding of how the chemical would cause cancer in humans. Analogy looks to see if similar chemicals are known to behave similarly and what is the available scientific data for those chemicals. In summary, there is a general consensus for methodologies to consider what causes cancer. Some criterion are absolutely required (e.g., consistency and not violating dose-response). Violating some of the principals will preclude the ability to support a causal relationship (e.g., temporality).

Target organ specificity: With only a few possible exceptions, chemicals exert their carcinogenic effect specifically to only one or a few organs. And in this case, as stated above, not all type of leukemia are the same. Based on clinical and molecular characteristics, it can be concluded that leukemia subtypes are different diseases with different targets. Target organ specificity is common and biologically plausible. Just as our organs are not interchangeable, the types of cancers that arise from them are different. Exposure routes allow for greater or lesser exposure at the cellular level in the target organ (i.e., different blood flow or blockage of exposure by the blood-brain barrier). Different tissues and cells express different metabolizing proteins such as cytochrome P450s, which are "intended" by evolution to be protective and aid excretion. Different tissues and cells also have different DNA damage, repair and programmed cell death capacities. Organs have different clearance mechanisms. There are some chemicals

that one would predict would be multiorgan carcinogens in humans, but are not. These include phenobarbital and caffeine. A clear example of target organ specificity is chemotherapy-related leukemia. As discussed above, there are chronic and acute leukemias, meaning that some people live for many years without or minimal treatment, while others are rapidly fatal. Depending on the cell type, the treatments are very different, as are the complications of the disease. Some chemotherapy can cause acute leukemia, but not chronic leukemia. Also, in the absence of other carcinogens such as radiation, chemotherapy does not induce other types of cancers.

HOW CANCER DEVELOPS AND THE LATENCY OF CANCER

Leukemia is a type of cancer of the blood cells. Cancer is a multistage process of normal growth, differentiation and development gone awry. It is driven by spontaneous and carcinogen-induced genetic and epigenetic events. The genes in the cells of our body are composed of deoxyribonucleic acids (DNA) that serve as a written language that programs a cell's function and provides for the building blocks to make proteins. Carcinogens bind to DNA and cause mutations and gross chromosome changes (e.g., chromosomal deletions, transfers of DNA from one chromosome to another, and chromosomal breaks) and/or alter gene expression (e.g., by affecting the switches for gene transcription). Cells normally replicate, differentiate and provide basic functions that sustain life, and then they die naturally. Mutated genes and damaged chromosomes can affect these basic functions, unless naturally existing safety mechanisms prevail. There are redundant DNA repair mechanisms, and cells also can be triggered to die if unrepairable DNA damage exists (a dead cell cannot go on to become cancer). If both of these mechanisms fail, however, cells may begin to replicate uncontrollably, and grow large, ultimately pushing out the normal cells and disturbing organ function. In this case, the CML cells can push out normally functioning cells from the bone marrow. The cells also can secrete chemicals that affect the function of other cells, for example, making bone marrow cells less sticky so that they can circulate at high levels in the blood. Cancer cells also secrete signal proteins that allow for their survival, such as blood vessel formation and allowing for metastases.

Cancer is actually a genetic disease comprising many mutations and damaged chromosomes. As carcinogens cause cumulative damage, the probability of "initiated" cells to transform into a malignancy increases, the odds of which are increased during repeated rounds of cell replication. The primary genes involved in driving the cancer process are protooncogenes and tumor suppressor genes. Protooncogenes are important to the regulatory mechanisms of growth, cell cycle and terminal differentiation. Activation of protooncogenes enhance the probability of neoplastic transformation, which can either be an early or late event. Tumor suppressor genes also code for products that regulate cell growth and terminal differentiation. However, they have the opposite effect by limiting growth and stimulating terminal differentiation. If inactivated, then the cell may grown uncontrollably or replicate without limits defined only by blood supply and space.

Cancer is mostly a disease of aging. This is likely to be due to the redundant and

protective mechanisms present in humans, e.g., metabolism, DNA repair and programmed cell death. While the DNA in our cells are constantly being exposed and affected by mutagens from birth, and before, most cancers do not develop until adulthood, and mostly much later. It is remarkable that we do not get all get cancer in childhood, if the presence of mutations, or single molecules were sufficient to cause cancer. Also, it is remarkable that persons we treat with chemotherapy or radiotherapy do not all get cancer. The fact that not everyone gets cancer at early ages also is consistent with a threshold effect for accumulated genetic damage (e.g., that one molecule cannot cause cancer, and that there needs to be enough exposure to cause multiple genetic abnormalities).

Recent data has highlighted the importance of the cancer stem cells, which are presumably derived from the stem cells within specific organs [83;84]. It is apparent that specific types of stem cells undergo the types of mutations described above, in specific cells that lead to cancers in target organs. Stem cells also secrete chemicals that affect the cells around them. Among the best studied are for leukemias, where the cells of origin that lead to very different types of leukemia are very different. There is data to show that there is little crossover from manipulating one type of stem cell to yield different types of leukemias or other cancers [83]

Latency: The issue of latency is important for the assessment of causality. It is an essential feature of the Hill criteria [64]. For individual risk assessment, and causality opinions in patients, it is obvious that exposure must precede the effect, or a causality opinion cannot be made. Latency generally refers to the time when exposure starts to the time a diagnosis is made. However, as stated above, cancer is a multistage genetic process so that this time frame would encompass a time period that includes early and late steps for carcinogenesis, and the time for symptoms to develop and be recognized as part of cancer. Latency for solid tumors is generally more than 20 years, and for some cancers are as long as 40 years. Cancers, when they first develop, are slow growing. Hematological malignancies can have a faster rate of growth than solid tumors and so the latency can be shorter than for solid tumors. However, the consideration for latency is imprecise, except for circumstances where there is a high dose and brief exposure, such as for atomic bomb exposures. Otherwise, there is generally considered a too brief latency time for which a dose and time to disease would be too short. On the other hand, to use a latency argument to support an opinion of causation is problematic, because for any individual, it is cumulative exposure that is required to trigger a clinical cancer to occur, and so it is impossible to know when the actual exposure began and ended. In this case, there is no airborne monitoring or personal exposure levels to document Mr. Christopher's alleged exposure.

CARCINOGEN CLASSIFICATION AND POPULATION-BASED RISK ASSESSMENT

The population-based risk assessment process, often more judgment and policymaking than science, is intended to protect the public health. The process utilizes the available scientific literature, beginning with a determination that there is sufficient evidence to warrant regulation of exposure. The decision to conduct risk assessment is based upon the classification of a potential chemical exposure as some type of carcinogen. This critical step provides great weight to animal studies, and allows for regulation in the absence of sufficient epidemiological data. This is done because our society wants chemicals regulated in the workplace and the environment, before we find out that a chemical is a hazard by causing cancer in humans. The regulation of a chemical, therefore, is based on criteria that are insufficient to allow a physician to advise a patient that their cancer has been caused by an exposure, that they have some future risk of cancer, or that they may need specific medical monitoring for the early detection of cancer.

Once a determination is made that a risk assessment should be performed, then study(s) are selected for the risk assessment modeling based on those that provide the best dose-response quantitative data. This does not always mean that there are consistent human studies to rely upon, or that the chosen studies are the best available, representative of the literature, or that there are not other better studies available (some of which might be null). Many times the experimental animal studies chosen use exposure scenarios substantially above what any human would be exposed to (e.g., by using maximally tolerated doses to animals) or animal models that will have different metabolic capacities. The modeling that is used, especially when based upon experimental animal data, incorporates many assumptions and safety factors to account for unknowns (e.g., our inability to know how to extrapolate animal data to humans). For example, many risk assessments assume that risks are linear, where one half the exposure will cause one-half the number of cancers. But this is not likely the case for low dose extrapolations at levels that humans are exposed, and for specific chemicals the actual shape of the curve for dose-response relationships are unknown. For the case of leukemia and benzene exposure, human epidemiological studies (and not case reports) are relied up to develop risk assessment estimates to protect workers and the public.

It is important to realize that regulatory and review processes, and the conclusions derived therein, are not applicable to the process of assessing past and future risk for individuals or groups of individuals such as in a litigation case. These agencies are classifying agents in order to prioritize which potential exposures should be considered for risk assessments and regulatory control. It is important to understand that these agencies consider population cancer risks (e.g., in thousands and millions of people) and do not provide conclusions regarding individual cancer risks (or for small groups of individuals). Their conclusions are focused on protecting the public health, i.e., to acknowledge that there are limitations in the scientific data and some risks might not be measurable. Their methods lead to an interpretation of data in ways that err on the side of

caution and assume worse risk than can exist. While this is an important process to protect humans before we learn whether a chemical causes cancer in people, these agency methods and findings are not appropriate to support a conclusion of cancer causation in a particular individual, or to predict risk in particular individuals, or to conclude whether the chemical is carcinogenic in humans at all. Moreover, a conclusion of possible or probable carcinogenic potential for one type of cancer in a target organ or leukemia does not imply that the chemical can cause cancer in other organs.

Several review and regulatory agencies have considered the leukemogenic potential for benzene. Table 2 provides the evaluations by the Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), the American Conference of Governmental Industrial Hygienists (ACGIH) and the National Toxicology Program (NTP).

Table 2
Carcinogenic Potential Designations by Review Agencies*

Substance	EPA	IARC	NTP	OSHA	NIOSH	ACGIH TLV
Benzene	A	1	K	Ca	Ca	A1

*Empty cells means no rating by agency

EPA (The EPA has used different classifications over the last 10 years.)

A –	Human carcinogen
B --	Probable human carcinogen: B1 Limited evidence from epidemiological studies, B2 Sufficient evidence from animal studies but inadequate for epidemiology
C --	Possible human carcinogen; limited evidence in animals
D --	Not classifiable; inadequate human and animal evidence, or no data available
K –	Known human carcinogen based on either epidemiological evidence or a combination of epidemiology and experimental evidence., treated as if they were known carcinogens based on some epidemiology and strong experimental evidence
L –	Likely to Produce cancer in humans bases on the weight of evidence, with high or low end of the weight. This may be given based on no epidemiological evidence and only experimental studies.
CBD –	Cannot be determined, but there is suggestive evidence
NL –	Not likely to be a carcinogen
CaH –	Carcinogenic to humans
S –	Suggestive, but not sufficient to assess human potential.
I –	Inadequate data

IARC	1 --	Carcinogenic in humans
	2A --	Probably carcinogenic to humans
	2B --	Possibly carcinogenic to humans
	3 --	Unclassifiable
	4 --	Probably not carcinogenic
NTP	K --	Known to be a human carcinogen
	R --	Reasonably anticipated to be a human carcinogen or sufficient evidence from animal studies
OSHA	Ca --	Carcinogen defined with no further categorization
NIOSH	Ca --	Carcinogen defined with no further categorization
ACGIH	A1 --	Confirmed human carcinogen
	A2 --	Suspected human carcinogen
	A3 --	Confirmed animal carcinogen
	A4 --	Not classifiable
	A5 --	Not suspected as a carcinogen

OVERVIEW OF OCCUPATION AND CHRONIC MYELOGENOUS LEUKEMIA RISK

Railroad Work

To start an evaluation of Mr. Christopher, it is best to examine what studies have been done in the railroad industry, and if any have been done that specifically assesses Mr. Christophers' type of work. There are numerous studies of workers assessing the railroad industry and leukemia risk, which consistently do not show an increased overall leukemia or CML risk. While these studies include workers from a diverse set of job classifications, and some of the focus has been on diesel exhaust or electromagnetic radiation as exposures for cancer risk, given that the allegations in this case are based in railroad work, it is reasonable to begin with an assessment of causality within this industry. If the plaintiff's experts were correct that benzene use in the railroad industry were sufficiently high to cause leukemia in general, and CML in particular, then studies of the railroad industry are most relevant to the present case. Because of the large number of studies, and the alleged benzene exposure, it would be expected to have some consistency for positive associations. Also, given the alleged exposure by plaintiff's experts, it would be reasonable to believe that scientists would have been reporting this and discussing benzene risks in the railroad industry. It should be noted that available studies include mechanics and other workers in railroad shops. I am aware of at least 9 publications for railroad work, none of which indicate an increased risk of leukemia [62;85-92] Some of these were quite large, for example, including 42,826 subjects, and specifically considered persons who worked in round houses and did similar work as Mr. Christopher [90]. In this Howe study, et al. [90], leukemia risk was actually statistically significantly decreased. Only one study that I am aware of reports an association for leukemia and railway work, but this positive study was considering electromagnetic radiation exposure, and not the type of work done by Mr. Christopher [93]. A similar study was null for leukemia [94]. It should be noted that I rely on some studies that do not directly discuss railroad work in the publication, but investigated occupational exposures where an association to railroad work would have been identified, if it existed, because the study methodology included coding for many occupations such as railroad work. While this may not be true for some, and I do not have specific evidence to show that this is the case in any particular study, it is a common practice among scientists to study many risk factors simultaneously and report only those findings that they consider significant. Importantly, there is not a single report that I am aware of that reports an association of CML and railroad work. Several have specifically investigated CML [88;95;96]. Thus, there is insufficient evidence to make the causal assumption that work in the railroad industry is associated with increased leukemia or CML risk. There is no evidence to conclude that the type of work done by Mr. Christopher increases leukemia risk, and none has been cited by plaintiff's experts.

Mr. Christopher testified that he was exposed to benzene, including pure benzene, 50% of the time. This exposure history of being exposed to benzene 50% of the time is inconsistent with

my understanding of the type of workplace for Mr. Christopher. The railroad industry is not known as one that regularly worked with benzene, although other types of solvents were commonly used. A literature search fails to identify benzene in solvents as a concerned risk in this industry [97;98]. I am not aware of any epidemiological study for cancer risk and the railroad industry that indicates an exposure to benzene as a concern. For example, benzene is not listed as an exposure in the 1983 publication of Howe and coworkers for 43,826 male pensioners who were exposed to fumes or other substances [90]. Some studies considering leukemia risk specifically stated that benzene was not used [93].

Benzene

There is sufficient epidemiological data to conclude that at sufficient exposure, benzene is a risk factor for acute myelogenous leukemia (AML). However, this cannot be simply extrapolated to conclude an increased risk for CML. Also, it is important to note that there is a dose-response effect for AML, which results in regulatory agencies making the determination for permissible level of workplace exposure. So, even if there were a hypothesis formulated by plaintiff's experts that benzene causes CML, because of the association for AML, there would need to be an accompanied assessment for how much exposure would cause CML in an individual (there is no quantitative data indicating how much benzene Mr. Christopher would have been exposed to, or how much are in railroad work places like his.) The levels of exposure to benzene in workers with potential high exposure to benzene have been documented for industries with increased leukemia risk, along with the variables that would modify the exposure levels [99].

There is a large potential for exposure to benzene in the general population [100;101], yet it is noted that leukemia is not a common cancer, especially CML. Importantly, if benzene at low doses contributed to leukemia risk, then leukemia would be a common disease. This is not the case, as only 9,000 Americans per year are diagnosed with AML. Thus, dose-response relationships for considering benzene-related cancer risks apply here, just as in causality assessments of any type.

Acute myeloid leukemia and benzene exposure: There is consistency in the literature for an association of benzene and AML [102-105]. However, there also is consistency for a dose-response relationship, where the workers who are at risk for leukemia are employed in industries with substantial and prolonged exposures to benzene. While there may be continuing debate about what level of exposure is needed to have a measurable increase in leukemia incidence [106;107], even those positive studies with lower workplace exposures exceed what would be conceivable for Mr. Christopher as understood for the type of place that he worked at [103;107-110]. For example, an extensively studied cohort is that of pliofilm workers, who made rubber film. Here, rubber would be dissolved in benzene and spread on a conveyer while the benzene evaporated. This potential direct exposure over a long period of time led to reporting of a

statistically significant increased AML incidence at 200 parts per million-years (i.e., 10 ppm for 20 years) [103;107;111]. Or, employment working directly with benzene as a petroleum worker required 15 years of employment before risk was measurably increased [108;109]. Risk tends to be higher with earlier years of exposure, where it is presumed that exposure levels for these highly exposed workers were even higher[106;112]. There are studies of workers with levels of exposure around 1 ppm not in the petroleum or rubber industry where there is no increase in leukemia risk [113].

The studies that provide the best evidence that benzene causes acute leukemia comes from heavily exposed workers in the rubber industry, shoemakers (through glue that contained up to 88% of benzene) and from China. In these occupations, other hematological toxic effects from benzene occur too, e.g., aplastic anemia and cytopenias. In a series of studies by Rinsky and coworkers, with updates, they reported on rubber hydrochloride workers through 1996 and 20 years of follow-up [110;114]. More than one-half of the cohort was deceased (976 of 1845). The overall risk of leukemia was 2.47 (95%CI=1.38, 4.07). Regarding a dose relationship and levels that exist below which a measurable increase in leukemia risk could be observed, in their lowest exposure group, which was 1 ppm day-30.99 ppm years, there was no statistically significant increase in risk (SMR=1.45; 95%CI=0.53, 3.31). Using the same cohort, Paxton and coworkers published data through 1987 [106;112;115]. Their risk estimates at the lower levels of exposure were lower. It was noted that there were no cases of leukemia in persons who began employment after 1950.

Hayes and coworkers conducted a large study of various occupations in China [116]. They included 74,828 workers, and reported an overall leukemia risk of 2.2 (95% CI= 1.1, 4.2). One finding included the risk decreasing after longer times from exposure, analogous to radiation or chemotherapy-induced leukemia. The Hayes series of papers indicate that the level of risk for AML and MDS combined is elevated at an average 10 ppm exposure (RR=5.8; 95% CI= 1.8, 18.8), and they note that this risk is higher than the Rinsky studies [103;116]. However, at less than 10 ppm, the risk was reported to be 2.0 (95% CI=0.6, 7.0), which was not statistically significant. For PPM years, the rates also were not statistically significant until >40 ppm-years. In this Chinese cohort, benzene exposure also was related to MDS risk [117].

Shoeworkers from Turkey and Italy have been reported to have an increased risk of leukemia. In the Aksoy series, it was reported that shoemakers had an incidence of 13.59 per 100,000 workers, which declined with the recognition of the disease and protection in the workplace [118]. The data also is suggestive of a drop off of cases after 10 years when exposure decreased. Dose-response data is limited from these series, although were reported as high as 110 ppm. There are examples of the consistency in the literature for workplaces that have been linked to increased leukemia risk, and a dose-response effect, where there is no measurable risk at the lowest levels of exposure. Costantini [119] provided data for other shoe workers, comparing their results with the Rinsky [120], and showed similarities where the increased risk was only statistically significant about 200 ppm-years, and for all levels of exposure, the

magnitude of the increased risk was similar. Other shoeworkers or manufacturers of rubber for shoes are positive [30;121;122].

The risk of leukemia can also be considered for the petroleum industry, where workers have continuous exposure to gasoline and other projects. Levels of total hydrocarbon exposure have been reported for different workers, such as those who distribute gasoline [123]. Regarding leukemia risk, there are some positive studies, while others are negative. A large meta-analysis by Wong and Raabe in 1995, based on 208,741 petroleum workers from the U.S. and Canada, with 4,665,361 person years, 56,441 deaths and 17 studies, found that the SMR for AML was only 0.96 (95% CI= 0.81, 1.13) [124]. Among the 17 studies, while some had elevated SMRs, none were statistically significant. Subset analyses for workers with more than 15 years of exposure were still null. Wong and coworkers studied petroleum workers in relation to gasoline exposure, known to contain benzene [125]. Based on 18,000 workers, this cohort included both land- and marine-based workers. The SMR for AML was 1.17 (95% CI=0.69, 1.85). The mean cumulative exposure to total hydrocarbons was 773 ppm-years. The mean duration of employment was 27.1 years. An analogous study by Schnatter, et al, focused on marketing and transportation workers within a petroleum company [126-128]. Among 34,597 workers, 5,041 were classified as exposed to finished products (e.g., diesel, gasoline and heating fuel). Leukemia risk was not elevated. In a separate publication, the subcategory of tank truck operators had an SMR of 3.35 (1.08, 7.81) for all types of leukemia, including chronic and acute [129]. This was based only on 5 deaths. Truckers were employed for more than 1 year. In another study of marketing and distribution workers, Rushton also did not find a clear association with AML [130]. Other studies of refinery workers are null [131;132].

I have considered that there are some petroleum industry studies that report positive associations, but there are many inconsistencies, and it is not clear that the literature demonstrates a dose-response relationship, which would be expected to demonstrate causality; some studies with lower exposures have positive risk estimates compared with studies that have higher exposures. Some studies might be positive because of higher levels of exposure. Australian petroleum workers were studied by Glass and coworkers in a nested case control study for 79 cases of leukemia and other hematological disorders, and 395 controls from an 18,000 person cohort [133] . They reported an OR for all leukemias at 1-2 ppm-years of 3.9 (95% CI=0.9, 17.1). For AML in particular, though, the risk was not increased until greater than 8 ppm-years. Although reporting increased risks at low levels of exposure, this study has been criticized in different ways, and so may overestimate risk [134;135]. A later re-analysis only found increased risks at greater than 16 ppm [136]. Divine and coworkers could not find an elevated SMR overall [137], but had borderline increased risks for workers employed before 1950 only (employment > 5 years) [138]. Christie and coworkers reported an SIR of 4.0 (95% CI= 1.6, 8.2) [139], although the SMR was not elevated [140]. In a study of petrol workers in Sweden and 9,000 men with 10 leukemia cases, a risk of 3.6 (95% CI=1.7, 6.6) was reported [141]. However, the level of benzene exposure was not studied (the authors noted that petrol contains 3-5% of benzene). These 10 workers included more than 5, typically about 15-20 years

of exposure, some were rubber workers or had other benzene exposures. (One case was reported to have worked on a tanker and was not a petrol station worker.) Importantly, the risk estimates for these studies are relatively large, indicating that most studies in the industry should have also been positive, because there are many other larger studies. Thus, it is more likely that these results were either random findings or were due to other exposures. There are many other null studies or some that just missed significance for the petroleum industry and acute leukemia [92;142-146], or some that are positive [147] that this industry probably has variability of exposure, accounting for some of the differences among studies.

Some other studies also consider benzene exposure as a risk factor for leukemia. Guenel, et. al., conducted a nested case control study of utility workers where benzene monitoring was available [148]. In this large cohort of 170,000 men, they had 72 total cases of leukemia, and matched them to 285 controls. While there was an association for leukemia and benzene, this only was measurable for persons with >16.8 ppm-years of exposure (3.6; 95% CI=1.1, 11.7), and even adjustment for this became nonsignficant. Exposure had to have occurred for more than 20 years. Studies of workers in chemical manufacturing plants have been null for AML and exposure to benzene [132;149].

Although in one study it has been suggested that the number of days with high levels of exposure is a better predictor of leukemia than duration of exposure [150]. In that positive study [150], among 4,417 chemical workers with exposures above 100 ppm for more than 40 days, there was a risk of 4.1, this was not statistically significant (95% CI=0.5, 4.9), was based on 2 deaths, and there was an SMR of zero for all levels below that.

Some other groups have lesser but measurable exposure to benzene, such as persons working with gasoline, e.g., gas station attendants, and persons who transport gasoline in the trucking or shipping industry. Petroleum industry workers are discussed above. It has been estimated that exposures for truck drivers and marine workers carrying gasoline have full-shift total hydrocarbon exposures of 9 to 14 ppm in truckers and 2 to 35 ppm for marine workers [123]. Using biomarkers, service station attendants increase their mean breath concentrations to benzene, xylene and toluene [151]. Levels of exposure to benzene, xylene and toluene for filling station attendants have been reported [152;153].

In a cohort study of 2,665 Italian filling station attendants, the SMR for leukemia was 56 [154]. In a study of 19,000 service station workers, the reported SIR was 1.3 (95% CI=0.7, 2.1). Other studies of service station attendants were null, or inferred null [92;153-156]. I am aware of only one positive study, by Schwartz [157]. In this study of service station workers, Schwartz reported a proportionate morality ratio for leukemia and aleukemia in service station workers living in the state of New Hampshire of 328 (95%CI=113, 951). However, this was based only on 3 cases, and one acute leukemia. Also, this was a death certificate only study, where the occupation was coded from the certificate, and it was a PMR study. Loomis and Savitz followed this study with a better designed case-control study of men in 16 states, although they still relied on death certificates [156]. In this study, the results were clearly null for service station workers

and leukemia overall, and for acute leukemia in particular. Using an ecological design considering the increased use of gasoline in European countries, it was predicted *a priori* that there would be an increase in leukemia, and specifically for AML [158], but none was found.

Infante and coworkers published a letter purporting the dangers of benzene in gasoline, citing three cases of leukemia in a group of garage workers residing in the District of Columbia [159]. This, however, was not an epidemiological study. Following this, Hunting and coworkers conducted a small study of garage workers, also within the District [160]. This study failed to find an association for employment with leukemia risk overall, but did claim an increased risk for leukemia and aleukemia in persons with the highest degree of exposures. The risk estimate was 9.26 based on 2 cases (histology not identified, but at most only one case had acute myelogenous leukemia). Another study reported a positive association for leukemia and mechanics, but the description of the data was limited including the type of mechanic, and CML was analyzed separately, but not reported. So likely was a null result [161]. In a study of automobile mechanics and gasoline service stations, Schwartz reported a proportionate morality ratio for leukemia and aleukemia in mechanics living in the state of New Hampshire of 178 (95% CI=81, 392) [157]. However, only 3 of 8 cases were acute leukemia for auto mechanics. Importantly, as noted above, this was a death certificate only study, where the occupation was coded from the certificate, and it was a PMR study. Loomis and Savitz followed this study with a better designed case-control study of men in 16 states [156]. In this study, the results were clearly null for mechanics and leukemia overall, and for acute leukemia in particular. Thus, the 3 positive publications provide insufficient evidence to conclude that vehicle mechanics are at increased risk for leukemia. In contrast to these studies, the overall literature does not support a causal relation between work as mechanics and leukemia, where I am aware of about 7 other studies that are null, or studies that can be inferred as null [86;92;156;162;163]. Review publications agree [164]. For example, in a large study across 16 states, including 615,834 deaths (5,147 leukemia deaths), and using 10 controls for each case, the odds ratio was 0.8 (95% CI=0.5. 1.1). Reviews of leukemia risk in vehicle mechanics do not conclude an increased leukemia risk [165]. Several studies have considered exposure in the context of leukemia subtype, but these are not supportive of an association either [165].

______***Chronic myelogenous leukemia and benzene risk:*** Most of the studies cited above only consider benzene and acute leukemia risk, or leukemia risk in general. There has been less study for CML, and the available literature does not support the causal opinion that benzene can cause CML at some dose [101;104]. In a review of 10 studies, only 2 were reported positive [104]. For example, in the series of publications from China, no statistical increase could be found, and thus these findings could be random chance [117;166;167]. Also, the shoe workers in Turkey were not reported to have an increased risk of CML, including for those with high levels of exposure and pancytopenia [118;168;169]. For the Rinsky and coworker studies, CML was not increased; in their group, there were only three reported cases, two of which worked less than 1 month and one had an ICD code for acute leukemia [110]. Other rubber worker studies are null for CML [104;121;170;171]. Another study of leukemia that reported levels of benzene

exposure do not find increased numbers of CML patients [133]. For the petroleum industry, where CML also was studied, null results has been reported [104;130;138;143;144;172], or inferred as null [129;173]. A large meta-analysis by Wong and Raabe in 1995, based on 208,741 petroleum workers from the U.S. and Canada, with 4,665,361 person years, 56,441 deaths, and 19 cohorts, found that the SMR for AML was only 0.89 (95% CI= 0.0.68, 1.15) [124]. Among the 19 cohorts reported, none had a statistically increased incidence of CML. Combined in different ways by geography, the meta-analysis did not indicate an increased risk, statistically significant or otherwise. Workers in the chemical industry and other industries with benzene exposure were null, or inferred as null for CML [108;148;150;174;175]. Persons exposed to gasoline vapors in the service station industry did not have reported increases in CML [153].

PLAINTIFF'S EXPERT REPORTS

Dr. Richard Lipsey: I have reviewed the report dated June 9, 2006. Dr. Lipsey claimed that benzene could cause CML, and that Mr. Christopher was exposed to levels that caused his leukemia. There was no discussion about how he came to a causal opinion, no discussion of different types of leukemia in relation to exposure risk, and no scientific references were cited (with one exception). Thus, there is no evidence that Dr. Lipsey used an acceptable method for coming to his opinions. He concluded a temporal relationship, but did not indicate that there was a 13 year gap between ceasing the railroad work and the onset of the CML, where there is some literature to show that acute leukemia risk decreases over time. He claims that 11 year latency has been reported. There is no data to support this opinion. Also, Dr. Lipsey apparently assumes that the alleged benzene exposure was occurring through 1993. Importantly, Dr. Lipsey acknowledges that CML is different from other types of leukemia.

Dr. Lipsey refers to a paper of submarine sailors for his evidence that benzene can cause CML, which is apparently a paper by Dean published in 1996 [176]. This paper clearly does not support Dr. Lipsey's causal opinion. It actually is a case report for a single case among submariners, and the author states that there is only an occasional case of CML in relation to benzene exposure reported in the literature. Also, while this single submariner might have been exposed to benzene, submariners are exposed to many types of indoor air pollution, and so the relationship is only hypothetical, at best. The paper derives a risk estimate based an this single case, which is then cited by Dr. Lipsey. Actually, Dr. Lipsey cited the maximal exposure estimate, although there is no evidence for an actual level experienced by Mr. Christopher. It is notable that the author concluded: "The increased risk involved in developing the rare CML is considered to be extremely small." Finally, there is no epidemiological study of submariners reporting an increased leukemia risk.

Dr. Lipsey, on the other hand, concludes that smoking does not cause CML, which he notes stopped for Mr. Christopher in 1990.

Dr. Bernard Goldstein: I have reviewed the report authored by Dr. Goldstein dated June 12, 2006. Dr. Goldstein concluded that there was a causal relationship between Mr. Christopher's reported benzene exposure and the development of his CML. Dr. Goldstein opined that the description of benzene use at Mr. Christopher's railroad workplace was credible, even though there is no data to support this, and the lack of evidence for an increased risk of leukemia in the railroad industry. If Dr. Goldstein were correct, and that there was real exposure at levels he assumes, then an increased risk for Mr. Christopher would have been identified in published studies of the railroad industry for leukemia in general, and CML in particular. Dr. Goldstein admits that there is "less conclusive epidemiological evidence" for a relationship for benzene-related CML among any literature and industry, and without such, any opinions extrapolated from studies that do not report results for CML is only speculative.

Dr. Goldstein discusses CML as developing from a stem cell, and attempts to analogize risks for all types of leukemia because these also derive from stem cells, albeit different ones. He does note in the literature that different types of leukemia would have different risks, for example chronic lymphocytic leukemia (CLL) [134]. In his publication, Dr. Goldstein concludes that benzene as a cause of CLL has not been conclusively shown, but this is inconsistent with the amount of available data leading to his conclusions for CML herein. Separately, it is not clear that Dr. Goldstein recognizes that the particular type of chromosomal abnormality in CML is not found in other types of leukemia, except in occasional cases of AML, and so the etiological link for Dr. Goldstein's opinion is tenuous. While there are some cytogenetic associations in workers exposed to benzene, as discussed by Dr. Goldstein, these also are not the type observed in CML [177].

Dr. Goldstein opines that because most cases of CML die from AML, the AML literature is applicable to CML, e.g., the CML increased risk is hidden in the AML literature. However, this is not defendable based an actual data or a consideration of reported chromosomal abnormalities for AML and benzene exposure (see above). Moreover, prospective cohort studies, such as the Australian Health Watch [133], would have identified the increasing cases of CML separate from AML. Dr. Goldstein admits the difficulties in formulating his opinions, and so, this leaves him only with a hypothesis and not a causality assessment.

The lack of quantitative exposure data for the workplace makes Dr. Goldstein's opinion problematic.

Dr. Goldstein discounts Mr. Christopher's long history for tobacco smoking as a causative factor in his disease. If Dr. Goldstein wants to consider all risks for AML as relevant for Mr. Christopher's causation assessment, it is inconsistent to conclude that the smoking was not a risk factor, or the major causative estimate. It is inconsistent to conclude that benzene can cause CML because it causes AML, and then disregard the scientific literature for smoking.

Arthur Frank: I have reviewed the report of Arthur Frank, dated February 20, 2006. He opined that Mr. Christopher's CML resulted from the alleged benzene exposure. There was no

methodology provided, or discussion of scientific data to support this opinion, so that it is impossible to comment on this report.

CONCLUSIONS

The following are my opinions and conclusions:

1. Mr. Christopher currently has chronic myelogenous leukemia. The latest medical records available to me indicate that he is in complete cytogenetic remission. Mr. Christopher's long term prognosis is excellent, although long term studies have not yet indicated what is the 10-year survival for persons who respond to Gleevec. He has additional treatment options, should the Gleevec treatment stop working, namely a higher dose of Gleevec and a number of new and promising investigational drugs. While stem cell transplantation is an option for some CML patients, it is likely that he will do well with the Gleevec, and he will be too elderly to tolerate a transplant. The survival figures at this point do not indicate the percent of CML patients who die from CML or other causes for 10 year survival, but given Mr. Christopher's age, it is more likely he will die from causes other than CML.

2. While some risk factors are known for CML, the causes for most patients remain obscure. This is true for Mr. Christopher. However, it would be improper to conclude that Mr. Christopher developed his CML because of work place exposures, because something must have caused it and there is a hypothesis that it might be benzene. In the clinic, we see cases like Mr. Christopher all the time, and we advise such patients that we do not know what causes CML. Clearly, there is no scientific consensus that benzene can cause CML, and none cited by plaintiff's experts.

3. It is alleged that Mr. Christopher developed his CML as a result of his railroad work and benzene exposure. While his described benzene exposure is not consistent with what would be expected for the railroad industry, there is no data to indicate that railroad workers are at an increased risk of CML, or leukemia in general. Thus, there remains the critical lack of data to support a causality claim in this case.

4. There is consistent data to show that sufficient exposure to benzene is a risk factor for acute myelogenous leukemia. However, CML is a different disease than AML. It looks different under a microscope, has a different chromosomal pattern, and is treated very differently. The only biological basis to analogize that benzene causes CML, because it causes AML, is that they are both hematological malignancies. However, there is not more data than this. For example, there is no data to show that a damaged stem cell can transform either into AML or CML. Because there is target organ specificity for carcinogenesis, it is equally possible, or more likely, that different carcinogens affect

different stem cells and thus we do not see an equal occurrence of AML and CML in benzene-exposed workers.

5. There is insufficient human data to opine that benzene causes a measurable increase in CML at any dose. There are many studies of persons with high levels of exposure to benzene, and these consistently do not show an increase in CML risk. While CML is less common than AML, and one may speculate that human studies fail to identify an increased CML risk because it is less common than CML and available studies lack sufficient power, we remain with the relationship for benzene exposure and CML causation as a hypothesis, and almost no human data. For an individual causation assessment, for example, in the courtroom or the clinic, one should not opine that it is more likely than not that Mr. Christopher developed his CML as a result of his workplace.

6. A fundamental tenet of toxicology and cancer risk is the dose-response relationship. Even if there was sufficient human data to opine that benzene can cause CML, there is no data to know what would be the dose sufficient to increase risk. In this case, there is no quantitative data about how much benzene Mr. Christopher would have been exposed to. His testimony is inconsistent with what the scientific literature says about his benzene exposure. Thus, it is impossible to opine that Mr. Christopher was exposed to a sufficient amount of benzene to cause CML, because that dose is unknown, if any, and we do not know what he was exposed to.

7. It has been opined that the scientific studies have not identified an increased risk for CML in heavily exposed benzene workers because CML transforms to AML, and so CML cases are underdiagnosed. First, no human studies for benzene exposed workers exist to support this speculation. Second, benzene-exposed workers have been extensively studied, and medical surveillance systems are established for them that would identify early cases of CML, so it is likely that if there were an increased risk of CML, occupational physicians and scientists would have identified this. Third, the number of AML cases that developed from CML that was not diagnosed, as evidence by AML with the Philadelphia chromosome, is very small. Thus, the hypothesis that the AML literature is hiding an increased CML risk is likely not correct.

8. There are well-established methods for assessing individual causality; the plaintiff's experts reports do not indicate that an acceptable methodology was used. Rather, there is fragmentary or no literature support, their opinions are speculative and/or hypothetical, they cannot support a consistent literature, and they are based on unknown dose-response relationships. This report provides citations and discussions for numerous studies relevant to Mr. Christopher. They are representative of the worlds' literature. Plaintiff's experts need to rely on scientific studies, and the studies cited herein do not provide the basis for a causal opinion.

9. Mr. Christopher was a heavy smoker. There is insufficient evidence to opine that Mr. Christopher developed his CML from smoking. There is sufficient evidence to conclude that cigarette smoking causes AML. Plaintiff's experts exclude smoking as a cause of Mr. Christopher's CML, but for them, this is inconsistent, because if they opine that benzene causes CML by way of a speculative AML analogy, then they must opine the same for smoking.

In summary, there is insufficient data to conclude that workplace exposures contributed to the development of Mr. Christopher's CML. Rather, he likely developed a CML of unknown etiology, which is typical for almost all patients with CML. The above opinions and conclusions are held by me a reasonable degree of medical and scientific certainty. If further information or data becomes available, I reserve the right to amend or alter my opinions. If there are further questions, please do not hesitate to contact me.

Sincerely,

Peter G. Shields, M.D.

Professor of Medicine and Oncology

Reference List

1. Spivak,J.L., Barosi,G., Tognoni,G., Barbui,T., Finazzi,G., Marchioli,R., and Marchetti,M. (2003) Chronic myeloproliferative disorders. *Hematology.(Am Soc.Hematol.Educ.Program.),*200-224.

2. De,K.K. and Cools,J. (2006) Chronic myeloproliferative disorders: a tyrosine kinase tale. *Leukemia*, **20**, 200-205.

3. Michiels,J.J., De,R.H., Berneman,Z., Van,B.D., Hebeda,K., Lam,K., and Schroyens,W. (2006) The 2001 World Health Organization and updated European clinical and pathological criteria for the diagnosis, classification, and staging of the Philadelphia chromosome-negative chronic myeloproliferative disorders. *Semin.Thromb.Hemost.*, **32**, 307-340.

4. Mauro,M.J. and Deininger,M.W. (2006) Chronic myeloid leukemia in 2006: a perspective. *Haematologica*, **91**, 152.

5. Jemal,A., Murray,T., Ward,E., Samuels,A., Tiwari,R.C., Ghafoor,A., Feuer,E.J., and Thun,M.J. (2005) Cancer statistics, 2005. *CA Cancer J Clin*, **55**, 10-30.

6. Quintas-Cardama,A. and Cortes,J.E. (2006) Chronic myeloid leukemia: diagnosis and treatment. *Mayo Clin.Proc.*, **81**, 973-988.

7. Johansson,B., Fioretos,T., and Mitelman,F. (2002) Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. *Acta Haematol.*, **107**, 76-94.

8. Babicka,L., Zemanova,Z., Pavlistova,L., Brezinova,J., Ransdorfova,S., Houskova,L., Moravcova,J., Klamova,H., and Michalova,K. (2006) Complex chromosomal rearrangements in patients with chronic myeloid leukemia. *Cancer Genet.Cytogenet.*, **168**, 22-29.

9. Sokal,J.E., Baccarani,M., Russo,D., and Tura,S. (1988) Staging and prognosis in chronic myelogenous leukemia. *Semin.Hematol.*, **25**, 49-61.

10. Mauro,M.J. and Maziarz,R.T. (2006) Stem cell transplantation in patients with chronic myelogenous leukemia: when should it be used? *Mayo Clin.Proc.*, **81**, 404-416.

11. Kantarjian,H.M., Talpaz,M., O'Brien,S., Jones,D., Giles,F., Garcia-Manero,G., Faderl,S., Ravandi,F., Rios,M.B., Shan,J., and Cortes,J. (2006) Survival Benefit with Imatinib Mesylate versus Interferon Alpha-Based Regimens in Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia. *Blood*.

12. Pierotti,B., Altieri,A., Talamini,R., Montella,M., Tavani,A., Negri,E., Franceschi,S., and La,V.C. (2005) Lifetime physical activity and prostate cancer risk. *Int.J.Cancer*, **114**, 639-642.

13. Simon,W., Segel,G.B., and Lichtman,M.A. (2006) Early allogeneic stem cell transplantation for chronic myelogenous leukemia in the imatinib era: A preliminary assessment. *Blood Cells Mol.Dis.* .

14. Chap,L. and Nimer,S.D. (1994) Chronic myelogenous leukemia following repeated radiation therapy for histiocytosis X. *Leuk.Lymphoma*, **12**, 315-316.

15. Inskip,P.D., Monson,R.R., Wagoner,J.K., Stovall,M., Davis,F.G., Kleinerman,R.A., and Boice,J.D., Jr. (1990) Leukemia following radiotherapy for uterine bleeding. *Radiat.Res.*, **122**, 107-119.

16. Shimon,I., Kneller,A., and Olchovsky,D. (1995) Chronic myeloid leukaemia following 131I treatment for thyroid carcinoma: a report of two cases and review of the literature. *Clin.Endocrinol.(Oxf)*, **43**, 651-654.

17. Preston,D.L., Kusumi,S., Tomonaga,M., Izumi,S., Ron,E., Kuramoto,A., Kamada,N., Dohy,H., Matsuo,T., and Matsui,T. (1994) Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987 [published erratum appears in Radiat Res 1994 Jul;139(1):129]. *Radiat.Res.*, **137**, S68-S97.

18. Kasim,K., Levallois,P., Abdous,B., Auger,P., and Johnson,K.C. (2005) Lifestyle factors and the risk of adult leukemia in Canada. *Cancer Causes Control*, **16**, 489-500.

19. Pan,S.Y., Johnson,K.C., Ugnat,A.M., Wen,S.W., and Mao,Y. (2004) Association of obesity and cancer risk in Canada. *Am.J.Epidemiol.*, **159**, 259-268.

20. Brown,L.M., Gibson,R., Blair,A., Burmeister,L.F., Schuman,L.M., Cantor,K.P., and Fraumeni,J.F., Jr. (1992) Smoking and risk of leukemia. *Am.J.Epidemiol.*, **135**, 763-768.

21. Adami,J., Nyren,O., Bergstrom,R., Ekbom,A., Engholm,G., Englund,A., and Glimelius,B. (1998) Smoking and the risk of leukemia, lymphoma, and multiple myeloma (Sweden). *Cancer Causes Control*, **9**, 49-56.

22. Kinlen,L.J. and Rogot,E. (1988) Leukaemia and smoking habits among United States veterans. *BMJ*, **297**, 657-659.

23. Kabat,G.C., Augustine,A., and Hebert,J.R. (1988) Smoking and adult leukemia: a case-control study. *J.Clin.Epidemiol.*, **41**, 907-914.

24. Doll,R. (1996) Cancers weakly related to smoking. *Br.Med Bull.*, **52**, 35-49.

25. Friedman,G.D. (1993) Cigarette smoking, leukemia, and multiple myeloma. *Ann.Epidemiol*, **3**, 425-428.

26. Herr,R., Ferguson,J., Myers,N., Rovira,D., and Robinson,W.A. (1990) Cigarette smoking, blast crisis, and survival in chronic myeloid leukemia. *Am.J.Hematol.*, **34**, 1-4.

27. Sandler,D.P., Shore,D.L., Anderson,J.R., Davey,F.R., Arthur,D., Mayer,R.J., Silver,R.T., Weiss,R.B., Moore,J.O., and Schiffer,C.A. (1993) Cigarette smoking and risk of acute leukemia: associations with morphology and cytogenetic abnormalities in bone marrow. *J Natl Cancer Inst.*, **85**, 1994-2003.

28. Nisse,C., Lorthois,C., Dorp,V., Eloy,E., Haguenoer,J.M., and Fenaux,P. (1995) Exposure to occupational and environmental factors in myelodysplastic syndromes. Preliminary results of a case-control study. *Leukemia*, **9**, 693-699.

29. Mills,P.K., Newell,G.R., Beeson,W.L., Fraser,G.E., and Phillips,R.L. (1990) History of cigarette smoking and risk of leukemia and myeloma: results from the Adventist health study [see comments]. *J Natl Cancer Inst.*, **82**, 1832-1836.

30. Mele,A., Stazi,M.A., Pulsoni,A., Visani,G., Monarca,B., Castelli,G., Rocchi,L., Avvisati,G., and Mandelli,F.

(1995) Epidemiology of acute promyelocytic leukemia. *Haematologica*, **80**, 405-408.

31. Kane,E.V., Roman,E., Cartwright,R., Parker,J., and Morgan,G. (1999) Tobacco and the risk of acute leukaemia in adults. *Br J Cancer*, **81**, 1228-1233.

32. Nisse,C., Haguenoer,J.M., Grandbastien,B., Preudhomme,C., Fontaine,B., Brillet,J.M., Lejeune,R., and Fenaux,P. (2001) Occupational and environmental risk factors of the myelodysplastic syndromes in the North of France. *Br J Haematol.*, **112**, 927-935.

33. Mele,A., Szklo,M., Visani,G., Stazi,M.A., Castelli,G., Pasquini,P., and Mandelli,F. (1994) Hair dye use and other risk factors for leukemia and pre-leukemia: a case-control study. Italian Leukemia Study Group. *Am.J.Epidemiol.*, **139**, 609-619.

34. Speer,S.A., Semenza,J.C., Kurosaki,T., and Anton-Culver,H. (2002) Risk factors for acute myeloid leukemia and multiple myeloma: a combination of GIS and case-control studies. *J Environ Health*, **64**, 9-16.

35. Pasqualetti,P., Festuccia,V., Acitelli,P., Collacciani,A., Giusti,A., and Casale,R. (1997) Tobacco smoking and risk of haematological malignancies in adults: a case-control study. *Br.J.Haematol.*, **97**, 659-662.

36. Linet,M.S., McLaughlin,J.K., Hsing,A.W., Wacholder,S., Co-Chien,H.T., Schuman,L.M., Bjelke,E., and Blot,W.J. (1991) Cigarette smoking and leukemia: results from the Lutheran Brotherhood Cohort Study. *Cancer Causes Control*, **2**, 413-417.

37. Stagnaro,E., Ramazzotti,V., Crosignani,P., Fontana,A., Masala,G., Miligi,L., Nanni,O., Neri,M., Rodella,S., Costantini,A.S., Tumino,R., Vigano,C., Vindigni,C., and Vineis,P. (2001) Smoking and hematolymphopoietic malignancies. *Cancer Causes Control*, **12**, 325-334.

38. Engeland,A., Andersen,A., Haldorsen,T., and Tretli,S. (1996) Smoking habits and risk of cancers other than lung cancer: 28 years' follow-up of 26,000 Norwegian men and women. *Cancer Causes Control*, **7**, 497-506.

39. Austin,H. and Cole,P. (1986) Cigarette smoking and leukemia. *J.Chronic.Dis.*, **39**, 417-421.

40. Brownson,R.C., Novotny,T.E., and Perry,M.C. (1993) Cigarette smoking and adult leukemia. A meta-analysis [see comments]. *Arch.Intern.Med*, **153**, 469-475.

41. Heath,C.W., Jr. (1990) Cigarette smoking and hematopoietic cancer. *J.Natl.Cancer Inst.*, **82**, 1800-1801.

42. Thomas,X. and Chelghoum,Y. (2004) Cigarette smoking and acute leukemia. *Leuk.Lymphoma*, **45**, 1103-1109.

43. Korte,J.E., Hertz-Picciotto,I., Schulz,M.R., Ball,L.M., and Duell,E.J. (2000) The contribution of benzene to smoking-induced leukemia. *Environ.Health Perspect.*, **108** , 333-339.

44. Pagano,L., Pulsoni,A., Tosti,M.E., Avvisati,G., Mele,L., Mele,M., Martino,B., Visani,G., Cerri,R., Di Bona,E., Invernizzi,R., Nosari,A., Clavio,M., Allione,B., Coser,P., Candoni,A., Levis,A., Camera,A., Melillo,L., Leone,G., and Mandelli,F. (2001) Clinical and biological features of acute myeloid leukaemia occurring as second malignancy: GIMEMA archive of adult acute leukaemia. *Br.J.Haematol.*, **112**, 109-117.

45. Leone,G., Mele,L., Pulsoni,A., Equitani,F., and Pagano,L. (1999) The incidence of secondary leukemias. *Haematologica*, **84**, 937-945.

46. Bennett,J.M. (1995) Secondary acute myeloid leukemia. *Leuk.Res*, **19**, 231-232.

47. Dann,E.J. and Rowe,J.M. (2001) Biology and therapy of secondary leukaemias. *Best.Pract.Res Clin Haematol.*, **14**, 119-137.

48. Blayney,D.W., Longo,D.L., Young,R.C., Greene,M.H., Hubbard,S.M., Postal,M.G., Duffey,P.L., and DeVita,V.T., Jr. (1987) Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. *N.Engl.J Med*, **316**, 710-714.

49. Boivin,J.F., Hutchison,G.B., Zauber,A.G., Bernstein,L., Davis,F.G., Michel,R.P., Zanke,B., Tan,C.T., Fuller,L.M., Mauch,P., and . (1995) Incidence of second cancers in patients treated for Hodgkin's disease. *J Natl Cancer Inst.*, **87**, 732-741.

50. Slovak,M.L., Kopecky,K.J., Cassileth,P.A., Harrington,D.H., Theil,K.S., Mohamed,A., Paietta,E., Willman,C.L., Head,D.R., Rowe,J.M., Forman,S.J., and Appelbaum,F.R. (2000) Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: a Southwest Oncology Group/Eastern Cooperative Oncology Group Study. *Blood*, **96**, 4075-4083.

51. Schoch,C., Kern,W., Schnittger,S., Hiddemann,W., and Haferlach,T. (2004) Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. *Leukemia*, **18**, 120-125.

52. Kern,W., Haferlach,T., Schnittger,S., Hiddemann,W., and Schoch,C. (2004) Prognosis in therapy-related acute myeloid leukemia and impact of karyotype. *J Clin Oncol*, **22**, 2510-2511.

53. Mehta,J., Powles,R., Treleaven,J., Swansbury,G.J., Kulkarni,S., Saso,R., Min,T., and Singhal,S. (1999) The impact of karyotype on remission rates in adult patients with de novo acute myeloid leukemia receiving high-dose cytarabine-based induction chemotherapy. *Leuk.Lymphoma*, **34**, 553-560.

54. Chang,H., Salma,F., Yi,Q.L., Patterson,B., Brien,B., and Minden,M.D. (2004) Prognostic relevance of immunophenotyping in 379 patients with acute myeloid leukemia. *Leuk.Res*, **28**, 43-48.

55. Visani,G., Bernasconi,P., Boni,M., Castoldi,G.L., Ciolli,S., Clavio,M., Cox,M.C., Cuneo,A., Del Poeta,G., Dini,D., Falzetti,D., Fanin,R., Gobbi,M., Isidori,A., Leoni,F., Liso,V., Malagola,M., Martinelli,G., Mecucci,C., Piccaluga,P.P., Petti,M.C., Rondelli,R., Russo,D., Sessarego,M., Specchia,G., Testoni,N., Torelli,G., Mandelli,F., and Tura,S. (2001) The prognostic value of cytogenetics is reinforced by the kind of induction/consolidation therapy in influencing the outcome of acute myeloid leukemia--analysis of 848 patients. *Leukemia*, **15**, 903-909.

56. Bacher,U., Kern,W., Schnittger,S., Hiddemann,W., Schoch,C., and Haferlach,T. (2005) Further correlations of morphology according to FAB and WHO classification to cytogenetics in de novo acute myeloid leukemia: a study on 2,235 patients. *Ann.Hematol.*, **84**, 785-791.

57. Klaus,M., Haferlach,T., Schnittger,S., Kern,W., Hiddemann,W., and Schoch,C. (2004) Cytogenetic profile in de novo acute myeloid leukemia with FAB subtypes M0, M1, and M2: a study based on 652 cases analyzed with morphology, cytogenetics, and fluorescence in situ hybridization. *Cancer Genet.Cytogenet.*, **155**, 47-56.

58. Mrozek,K., Heerema,N.A., and Bloomfield,C.D. (2004) Cytogenetics in acute leukemia. *Blood Rev.*, **18**, 115-136.

59. Felix,C.A. (1998) Secondary leukemias induced by topoisomerase-targeted drugs. *Biochim.Biophys.Acta*, **1400**, 233-255.

60. Andersen,M.K., Johansson,B., Larsen,S.O., and Pedersen-Bjergaard,J. (1998) Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. *Haematologica*, **83**, 483-488.

61. Pedersen-Bjergaard,J., Brondum-Nielsen,K., Karle,H., and Johansson,B. (1997) Chemotherapy-related - late occurring - Philadelphia chromosome in AML, ALL and CML. Similar events related to treatment with DNA topoisomerase II inhibitors? *Leukemia*, **11**, 1571-1574.

62. Richardson,S., Zittoun,R., Bastuji-Garin,S., Lasserre,V., Guihenneuc,C., Cadiou,M., Viguie,F., and Laffont-Faust,I. (1992) Occupational risk factors for acute leukaemia: a case-control study. *Int.J.Epidemiol.*, **21**, 1063-1073.

63. Crane,M.M., Strom,S.S., Halabi,S., Berman,E.L., Fueger,J.J., Spitz,M.R., and Keating,M.J. (1996) Correlation between selected environmental exposures and karyotype in acute myelocytic leukemia. *Cancer Epidemiol Biomarkers Prev*, **5**, 639-644.

64. Hill,A.B. (1965) The environment and disease: association or causation. *Proc.Royal Soc.Med.*, **58**, 295-300.

65. Rothman,K.J. and Greenland,S. (2005) Causation and causal inference in epidemiology. *Am J Public Health*, **95 Suppl 1**, S144-S150.

66. Olsen,J. (2003) What characterises a useful concept of causation in epidemiology? *J Epidemiol Community Health* , **57**, 86-88.

67. Colston,K.W. and Hansen,C.M. (2002) Mechanisms implicated in the growth regulatory effects of vitamin D in breast cancer. *Endocr.Relat Cancer*, **9**, 45-59.

68. Lipton,R. and Odegaard,T. (2005) Causal thinking and causal language in epidemiology: it's in the details. *Epidemiol Perspect.Innov.*, **2**, 8.

69. Advisory Committee to the Surgeon General of the Public Health Service, Washington DC. U.S. Public Health Service, Smoking and health. publication no.1103. 1964. Washington, DC, U.S.Department of Health,Education and Welfare.
Ref Type: Report

70. Svoboda,D.J., Reddy,J.K., and Harris,C.C. (1970) Invasive tumors induced in rats with Actinomycin D. *Cancer Res.*, **30**, 2271-2279.

71. Diorio,C., Berube,S., Byrne,C., Masse,B., Hebert-Croteau,N., Yaffe,M., Cote,G., Pollak,M., and Brisson,J. (2006) Influence of insulin-like growth factors on the strength of the relation of vitamin D and calcium intakes to mammographic breast density. *Cancer Res*, **66**, 588-597.

72. Doll,R., Peto,R., Wheatley,K., Gray,R., and Sutherland,I. (1994) Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*, **309**, 901-911.

73. Stellman,S.D. and Garfinkel,L. (1989) Lung cancer risk is proportional to cigarette tar yield: evidence from a prospective study. *Prev.Med*, **18**, 518-525.

74. Garfinkel,L. and Stellman,S.D. (1988) Smoking and lung cancer in women: findings in a prospective study. *Cancer Res*, **48**, 6951-6955.

75. McLaughlin,J.K., Hrubec,Z., Blot,W.J., and Fraumeni,J.F., Jr. (1995) Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. *Int.J Cancer*, **60**, 190-193.

76. Akiba,S. and Hirayama,T. (1990) Cigarette smoking and cancer mortality risk in Japanese men and women--results from reanalysis of the six-prefecture cohort study data. *Environ Health Perspect.*, **87**, 19-26.

77. Hammond,E.C. and Horn,D. (1988) Smoking and death rates--report on forty-four months of follow-up of 187,783 men. By E. Cuyler Hammond and Daniel Horn, 1958 [classical article]. *CA Cancer J Clin.*, **38**, 28-58.

78. International Agency for reseach on cancer (2004) Tobacco smoke and involuntary smoking. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. IARC, Lyon, France.

79. Weir,J.M. and Dunn,J.E., Jr. (1970) Smoking and mortality: a prospective study. *Cancer*, **25**, 105-112.

80. Kuller,L.H., Ockene,J.K., Meilahn,E., Wentworth,D.N., Svendsen,K.H., and Neaton,J.D. (1991) Cigarette smoking and mortality. MRFIT Research Group. *Prev.Med*, **20**, 638-654.

81. Potter,J.D., Sellers,T.A., Folsom,A.R., and McGovern,P.G. (1992) Alcohol, beer, and lung cancer in postmenopausal women. The Iowa Women's Health Study. *Ann.Epidemiol*, **2**, 587-595.

82. Tverdal,A., Thelle,D., Stensvold,I., Leren,P., and Bjartveit,K. (1993) Mortality in relation to smoking history: 13 years' follow-up of 68,000 Norwegian men and women 35-49 years. *J Clin Epidemiol*, **46**, 475-487.

83. Wang,J.C. and Dick,J.E. (2005) Cancer stem cells: lessons from leukemia. *Trends Cell Biol.*, **15**, 494-501.

84. Soltysova,A., Altanerova,V., and Altaner,C. (2005) Cancer stem cells. *Neoplasma*, **52**, 435-440.

85. Costantini,A.S., Miligi,L., Kriebel,D., Ramazzotti,V., Rodella,S., Scarpi,E., Stagnaro,E., Tumino,R., Fontana,A., Masala,G., Vigano,C., Vindigni,C., Crosignani,P., Benvenuti,A., and Vineis,P. (2001) A multicenter case-control study in Italy on hematolymphopoietic neoplasms and occupation. *Epidemiology*, **12**, 78-87.

86. Dubrow,R. and Wegman,D.H. (1984) Cancer and occupation in Massachusetts: a death certificate study. *Am.J Ind.Med*, **6**, 207-230.

87. Fincham,S., MacMillan,A., Turner,D., and Berkel,J. (1993) Occupational risks for cancer in Alberta. *Health Rep.*, **5**, 67-72.

88. Floderus,B., Tornqvist,S., and Stenlund,C. (1994) Incidence of selected cancers in Swedish railway workers, 1961-79. *Cancer Causes Control*, **5**, 189-194.

89. Garshick,E., Schenker,M.B., Munoz,A., Segal,M., Smith,T.J., Woskie,S.R., Hammond,S.K., and Speizer,F.E. (1988) A retrospective cohort study of lung cancer and diesel exhaust exposure in railroad workers. *Am Rev.Respir.Dis.*, **137**, 820-825.

90. Howe,G.R., Fraser,D., Lindsay,J., Presnal,B., and Yu,S.Z. (1983) Cancer mortality (1965-77) in relation to diesel fume and coal exposure in a cohort of retired railway workers. *J Natl Cancer Inst.*, **70**, 1015-1019.

91. Schenker,M.B., Smith,T., Munoz,A., Woskie,S., and Speizer,F.E. (1984) Diesel exposure and mortality among railway workers: results of a pilot study. *Br J Ind.Med*, **41**, 320-327.

92. Williams,R.R., Stegens,N.L., and Goldsmith,J.R. (1977) Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. *J Natl Cancer Inst.*, **59**, 1147-1185.

93. Minder,C.E. and Pfluger,D.H. (2001) Leukemia, brain tumors, and exposure to extremely low frequency electromagnetic fields in Swiss railway employees. *Am.J.Epidemiol.*, **153**, 825-835.

94. Tynes,T., Jynge,H., and Vistnes,A.I. (1994) Leukemia and brain tumors in Norwegian railway workers, a nested case- control study. *Am J Epidemiol*, **139**, 645-653.

95. Alfredsson,L., Hammar,N., and Karlehagen,S. (1996) Cancer incidence among male railway engine-drivers and conductors in Sweden, 1976-90. *Cancer Causes Control*, **7**, 377-381.

96. Gygi,S.P., Rist,B., Gerber,S.A., Turecek,F., Gelb,M.H., and Aebersold,R. (1999) Quantitative analysis of complex protein mixtures using isotope-coded affinity tags. *Nat.Biotechnol.*, **17**, 994-999.

97. Madl,A.K. and Paustenbach,D.J. (2002) Airborne concentrations of benzene and mineral spirits (stoddard solvent) during cleaning of a locomotive generator and traction motor. *J.Toxicol.Environ.Health A*, **65**, 1965-1979.

98. Frumkin,H., Ducatman,A., and Kirkland,K. (1997) Solvent exposure in the railroad industry. *J Occup.Environ Med* , **39**, 926-930.

99. Lewis,S.J., Bell,G.M., Cordingley,N., Pearlman,E.D., and Rushton,L. (1997) Retrospective estimation of exposure to benzene in a leukaemia case- control study of petroleum marketing and distribution workers in the United Kingdom. *Occup.Environ Med*, **54**, 167-175.

100. Wallace,L. (1996) Environmental exposure to benzene: an update. *Environ.Health Perspect.*, **104 Suppl 6**, 1129-1136.

101. Pyatt,D. (2004) Benzene and hematopoietic malignancies. *Clin.Occup.Environ.Med.*, **4**, 529-55, vii.

102. Kogevinas,M., Sala,M., Boffetta,P., Kazerouni,N., Kromhout,H., and Hoar-Zahm,S. (1998) Cancer risk in the rubber industry: a review of the recent epidemiological evidence [see comments]. *Occup.Environ Med*, **55**, 1-12.

103. Hayes,R.B., Songnian,Y., Dosemeci,M., and Linet,M. (2001) Benzene and lymphohematopoietic malignancies in humans. *Am J Ind.Med*, **40**, 117-126.

104. Schnatter,A.R., Rosamilia,K., and Wojcik,N.C. (2005) Review of the literature on benzene exposure and leukemia subtypes. *Chem.Biol.Interact.*, **153-154**, 9-21.

105. Descatha,A., Jenabian,A., Conso,F., and Ameille,J. (2005) Occupational exposures and haematological malignancies: overview on human recent data. *Cancer Causes Control*, **16**, 939-953.

106. Paxton,M.B., Chinchilli,V.M., Brett,S.M., and Rodricks,J.V. (1994) Leukemia risk associated with benzene exposure in the pliofilm cohort. II. Risk estimates. *Risk Anal*, **14**, 155-161.

107. Rinsky,R.A., Smith,A.B., Hornung,R., Filloon,T.G., Young,R.J., Okun,A.H., and Landrigan,P.J. (1987) Benzene and leukemia. An epidemiologic risk assessment. *N.Engl.J Med*, **316**, 1044-1050.

108. Ireland,B., Collins,J.J., Buckley,C.F., and Riordan,S.G. (1997) Cancer mortality among workers with benzene exposure. *Epidemiology*, **8**, 318-320.

109. Bertazzi,P.A., Pesatori,A.C., Zocchetti,C., and Latocca,R. (1989) Mortality study of cancer risk among oil

refinery workers. *Int.Arch.Occup.Environ Health*, **61**, 261-270.

110. Rinsky,R.A., Hornung,R.W., Silver,S.R., and Tseng,C.Y. (2002) Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment. *Am J Ind.Med*, **42**, 474-480.

111. Wong,O. (1995) Risk of acute myeloid leukaemia and multiple myeloma in workers exposed to benzene [see comments]. *Occup.Environ Med*, **52**, 380-384.

112. Paxton,M.B., Chinchilli,V.M., Brett,S.M., and Rodricks,J.V. (1994) Leukemia risk associated with benzene exposure in the pliofilm cohort: I. Mortality update and exposure distribution. *Risk Anal*, **14**, 147-154.

113. Hurley,J.F., Cherrie,J.W., and Maclaren,W. (1991) Exposure to benzene and mortality from leukaemia: results from coke oven and other coal product workers. *Br.J.Ind.Med.*, **48**, 502-503.

114. Silver,S.R., Rinsky,R.A., Cooper,S.P., Hornung,R.W., and Lai,D. (2002) Effect of follow-up time on risk estimates: a longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort. *Am J Ind.Med*, **42**, 481-489.

115. Paxton,M.B. (1996) Leukemia risk associated with benzene exposure in the Pliofilm cohort. *Environ Health Perspect.*, **104 Suppl 6**, 1431-1436.

116. Hayes,R.B., Yin,S.N., Dosemeci,M., Li,G.L., Wacholder,S., Travis,L.B., Li,C.Y., Rothman,N., Hoover,R.N., and Linet,M.S. (1997) Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group [see comments]. *J Natl Cancer Inst.*, **89**, 1065-1071.

117. Hayes,R.B., Yin,S., Rothman,N., Dosemeci,M., Li,G., Travis,L.T., Smith,M.T., and Linet,M.S. (2000) Benzene and lymphohematopoietic malignancies in China. *J Toxicol Environ Health A*, **61**, 419-432.

118. Aksoy,M. (1985) Malignancies due to occupational exposure to benzene. *Am J Ind.Med*, **7**, 395-402.

119. Seniori,C.A., Quinn,M., Consonni,D., and Zappa,M. (2003) Exposure to benzene and risk of leukemia among shoe factory workers. *Scand J Work Environ Health*, **29**, 51-59.

120. Rinsky,R.A., Young,R.J., and Smith,A.B. (1981) Leukemia in benzene workers. *Am J Ind.Med*, **2**, 217-245.

121. Norseth,T., Andersen,A., and Giltvedt,J. (1983) Cancer incidence in the rubber industry in Norway. *Scand J Work Environ Health*, **9 Suppl 2**, 69-71.

122. Fu,H., Demers,P.A., Costantini,A.S., Winter,P., Colin,D., Kogevinas,M., and Boffetta,P. (1996) Cancer mortality among shoe manufacturing workers: an analysis of two cohorts. *Occup.Environ Med*, **53**, 394-398.

123. Smith,T.J., Hammond,S.K., and Wong,O. (1993) Health effects of gasoline exposure. I. Exposure assessment for U.S. distribution workers. *Environ Health Perspect.*, **101 Suppl 6**, 13-21.

124. Wong,O. and Raabe,G.K. (1995) Cell-type-specific leukemia analyses in a combined cohort of more than 208,000 petroleum workers in the United States and the United Kingdom, 1937-1989. *Regul.Toxicol.Pharmacol.*, **21**, 307-321.

125. Wong,O., Trent,L., and Harris,F. (1999) Nested case-control study of leukaemia, multiple myeloma, and kidney cancer in a cohort of petroleum workers exposed to gasoline. *Occup Environ Med*, **56**, 217-221.

126. Schnatter,A.R., Theriault,G., Katz,A.M., Thompson,F.S., Donaleski,D., and Murray,N. (1992) A retrospective mortality study within operating segments of a petroleum company. *Am.J Ind.Med*, **22**, 209-229.

127. Schnatter,A.R., Armstrong,T.W., Thompson,L.S., Nicolich,M.J., Katz,A.M., Huebner,W.W., and Pearlman,E.D. (1996) The relationship between low-level benzene exposure and leukemia in Canadian petroleum distribution workers. *Environ.Health Perspect.*, **104 Suppl 6**, 1375-1379.

128. Schnatter,A.R., Armstrong,T.W., Nicolich,M.J., Thompson,F.S., Katz,A.M., Huebner,W.W., and Pearlman,E.D. (1996) Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occup.Environ Med*, **53**, 773-781.

129. Schnatter,A.R., Katz,A.M., Nicolich,M.J., and Theriault,G. (1993) A retrospective mortality study among Canadian petroleum marketing and distribution workers. *Environ Health Perspect.*, **101 Suppl 6**, 85-99.

130. Rushton,L. and Romaniuk,H. (1997) A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom [see comments]. *Occup.Environ Med*, **54**, 152-166.

131. Pukkala,E. (1998) Cancer incidence among Finnish oil refinery workers, 1971-1994. *J Occup Environ Med*, **40**, 675-679.

132. Marsh,G.M., Enterline,P.E., and McCraw,D. (1991) Mortality patterns among petroleum refinery and chemical plant workers. *Am J Ind.Med*, **19**, 29-42.

133. Glass,D.C., Gray,C.N., Jolley,D.J., Gibbons,C., Sim,M.R., Fritschi,L., Adams,G.G., Bisby,J.A., and Manuell,R. (2003) Leukemia risk associated with low-level benzene exposure. *Epidemiology*, **14**, 569-577.

134. Goldstein,B. (2004) Benzene exposure and leukemia. *Epidemiology*, **15**, 509-510.

135. Schnatter,A.R. (2004) Benzene exposure and leukemia. *Epidemiology*, **15**, 509-1.

136. Glass,D.C., Gray,C.N., Jolley,D.J., Gibbons,C., and Sim,M.R. (2005) Health Watch exposure estimates: do they underestimate benzene exposure? *Chem.Biol.Interact.*, **153-154**, 23-32.

137. Divine,B.J., Hartman,C.M., and Wendt,J.K. (1999) Update of the Texaco mortality study 1947-93: Part I. Analysis of overall patterns of mortality among refining, research, and petrochemical workers. *Occup.Environ Med*, **56**, 167-173.

138. Divine,B.J., Hartman,C.M., and Wendt,J.K. (1999) Update of the Texaco mortality study 1947-93: Part II. Analyses of specific causes of death for white men employed in refining, research, and petrochemicals [see comments]. *Occup.Environ Med*, **56** , 174-180.

139. Christie,D., Robinson,K., Gordon,I., and Bisby,J. (1991) A prospective study in the Australian petroleum industry. II. Incidence of cancer. *Br.J Ind.Med*, **48**, 511-514.

140. Christie,D., Robinson,K., Gordon,I., and Bisby,J. (1991) A prospective study in the Australian petroleum industry. I. Mortality. *Br.J Ind.Med*, **48**, 507-510.

141. Jakobsson,R., Ahlbom,A., Bellander,T., and Lundberg,I. (1993) Acute myeloid leukemia among petrol station attendants. *Arch Environ Health*, **48**, 255-259.

142. Theriault,G. and Provencher,S. (1987) Mortality study of oil refinery workers: five-year follow-up. *J*

Occup.Med, **29**, 357-360.

143. Gun,R.T., Pratt,N.L., Griffith,E.C., Adams,G.G., Bisby,J.A., and Robinson,K.L. (2004) Update of a prospective study of mortality and cancer incidence in the Australian petroleum industry. *Occup Environ Med*, **61**, 150-156.

144. Lewis,R.J., Schnatter,A.R., Katz,A.M., Thompson,F.S., Murray,N., Jorgensen,G., and Theriault,G. (2000) Updated mortality among diverse operating segments of a petroleum company. *Occup Environ Med*, **57**, 595-604.

145. Hanis,N.M., Holmes,T.M., Shallenberger,G., and Jones,K.E. (1982) Epidemiologic study of refinery and chemical plant workers. *J Occup.Med*, **24**, 203-212.

146. Lewis,R.J., Schnatter,A.R., Drummond,I., Murray,N., Thompson,F.S., Katz,A.M., Jorgensen,G., Nicolich,M.J., Dahlman,D., and Theriault,G. (2003) Mortality and cancer morbidity in a cohort of Canadian petroleum workers. *Occup Environ Med*, **60**, 918-928.

147. Thomas,T.L., Decoufle,P., and Moure-Eraso,R. (1980) Mortality among workers employed in petroleum refining and petrochemical plants. *J Occup.Med*, **22**, 97-103.

148. Guenel,P., Imbernon,E., Chevalier,A., Crinquand-Calastreng,A., and Goldberg,M. (2002) Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers. *Am J Ind.Med*, **42**, 87-97.

149. Ott,M.G., Teta,M.J., and Greenberg,H.L. (1989) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. *Am J Ind.Med*, **16**, 631-643.

150. Collins,J.J., Ireland,B., Buckley,C.F., and Shepperly,D. (2003) Lymphohaematopoeitic cancer mortality among workers with benzene exposure. *Occup Environ Med*, **60**, 676-679.

151. Jo,W.K., Lee,J.W., and Shin,D.C. (2004) Exposure to volatile organic compounds in residences adjacent to dyeing industrial complex. *Int.Arch.Occup.Environ.Health*, **77**, 113-120.

152. Lagorio,S., Forastiere,F., Iavarone,I., Vanacore,N., Fuselli,S., and Carere,A. (1993) Exposure assessment in a historical cohort of filling station attendants. *Int.J Epidemiol*, **22 Suppl 2**, S51-S56.

153. Lynge,E., Andersen,A., Nilsson,R., Barlow,L., Pukkala,E., Nordlinder,R., Boffetta,P., Grandjean,P., Heikkila,P., Horte,L.G., Jakobsson,R., Lundberg,I., Moen,B., Partanen,T., and Riise,T. (1997) Risk of cancer and exposure to gasoline vapors. *Am.J.Epidemiol.*, **145**, 449-458.

154. Lagorio,S., Forastiere,F., Iavarone,I., Rapiti,E., Vanacore,N., Perucci,C.A., and Carere,A. (1994) Mortality of filling station attendants. *Scand J Work Environ Health*, **20**, 331-338.

155. Siemiatycki,J., Gerin,M., Stewart,P., Nadon,L., Dewar,R., and Richardson,L. (1988) Associations between several sites of cancer and ten types of exhaust and combustion products. Results from a case-referent study in Montreal. *Scand J Work Environ Health*, **14**, 79-90.

156. Loomis,D.P. and Savitz,D.A. (1991) Occupation and leukemia mortality among men in 16 states: 1985-1987. *Am.J.Ind.Med.*, **19**, 509-521.

157. Schwartz,E. (1987) Proportionate mortality ratio analysis of automobile mechanics and gasoline service station workers in New Hampshire. *Am J Ind.Med*, **12**, 91-99.

158. Terstegge,C.W., Swaen,G.M., Slangen,J.J., and Van Vliet,C. (1995) Mortality Patterns among Commercial Painters in The Netherlands. *Int.J Occup Environ Health*, **1**, 303-310.

159. Infante,P.F., Schwartz,E., and Cahill,R. (1990) Benzene in petrol: a continuing hazard. *Lancet*, **336**, 814-815.

160. Hunting,K.L., Longbottom,H., Kalavar,S.S., Stern,F., Schwartz,E., and Welch,L.S. (1995) Haematopoietic cancer mortality among vehicle mechanics. *Occup.Environ Med*, **52**, 673-678.

161. Brownson,R.C. and Reif,J.S. (1988) A cancer registry-based study of occupational risk for lymphoma, multiple myeloma and leukaemia. *Int.J Epidemiol*, **17**, 27-32.

162. Blair,A., Walrath,J., and Rogot,E. (1985) Mortality patterns among U.S. veterans by occupation. I. Cancer. *J Natl.Cancer Inst.*, **75**, 1039-1047.

163. Hansen,E.S. (1989) Mortality of auto mechanics. A ten-year follow-up. *Scand.J.Work Environ.Health*, **15**, 43-46.

164. Hotz,P. and Lauwerys,R.R. (1997) Hematopoietic and lymphatic malignancies in vehicle mechanics. *Crit Rev.Toxicol.*, **27**, 443-494.

165. Saverin,R., Braunlich,A., Dahmann,D., Enderlein,G., and Heuchert,G. (1999) Diesel exhaust and lung cancer mortality in potash mining. *Am J Ind.Med*, **36**, 415-422.

166. Travis,L.B., Li,C.Y., Zhang,Z.N., Li,D.G., Yin,S.N., Chow,W.H., Li,G.L., Dosemeci,M., Blot,W., Fraumeni,J.F., Jr., and . (1994) Hematopoietic malignancies and related disorders among benzene-exposed workers in China. *Leuk.Lymphoma*, **14**, 91-102.

167. Yin,S.N., Hayes,R.B., Linet,M.S., Li,G.L., Dosemeci,M., Travis,L.B., Li,C.Y., Zhang,Z.N., Li,D.G., Chow,W.H., Wacholder,S., Wang,Y.Z., Jiang,Z.L., Dai,T.R., Zhang,W.Y., Chao,X.J., Ye,P.Z., Kou,Q.R., Zhang,X.C., Lin,X.F., Meng,J.F., Ding,C.Y., Zho,J.S., and Blot,W.J. (1996) A cohort study of cancer among benzene-exposed workers in China: overall results. *Am.J.Ind.Med.*, **29**, 227-235.

168. Aksoy,M. and Erdem,S. (1978) Followup study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic exposure to benzene. *Blood*, **52**, 285-292.

169. Aksoy,M., Erdem,S., and Dincol,G. (1976) Types of leukemia in chronic benzene poisoning. A study in thirty-four patients. *Acta Haematol.*, **55**, 65-72.

170. Ke,L. and Shunzhang,Y. (1999) Economic status and occupational correlates of stomach cancer in the rubber industry. *Int.J Occup Med Environ Health*, **12**, 345-352.

171. Vigliani,E.C. (1976) Leukemia associated with benzene exposure. *Ann.N.Y.Acad.Sci.*, **271**, 143-151.

172. Wongsrichanalai,C., Delzell,E., and Cole,P. (1989) Mortality from leukemia and other diseases among workers at a petroleum refinery. *J.Occup.Med*, **31**, 106-111.

173. Bloemen,L.J., Youk,A., Bradley,T.D., Bodner,K.M., and Marsh,G. (2004) Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. *Occup.Environ.Med.*, **61**, 270-274.

174. Massoudi,B.L., Talbott,E.O., Day,R.D., Swerdlow,S.H., Marsh,G.M., and Kuller,L.H. (1997) A case-control study of hematopoietic and lymphoid neoplasms: the role of work in the chemical industry [see comments]. *Am.J Ind.Med*, **31**, 21-27.

175. Bond,G.G., McLaren,E.A., Baldwin,C.L., and Cook,R.R. (1986) An update of mortality among chemical workers exposed to benzene. *Br.J Ind.Med*, **43**, 685-691.

176. Dean,M.R. (1996) Benzene exposure in Royal Naval submarines. *J R.Soc.Med*, **89**, 286P-288P.

177. Smith,M.T., Zhang,L., Wang,Y., Hayes,R.B., Li,G., Wiemels,J., Dosemeci,M., Titenko-Holland,N., Xi,L., Kolachana,P., Yin,S., and Rothman,N. (1998) Increased translocations and aneusomy in chromosomes 8 and 21 among workers exposed to benzene. *Cancer Res.*, **58**, 2176-2181.

Peter G. Shields, M.D.
List of Testimony Previous 5 Years
July 21, 2006

8/13/01	Cronise v. Norfolk Southern - deposition
10/18/01	Wilson v. CSX - deposition
11/05/01	Comer v. - deposition
9/24/02	Rivera v. Philip Morris - deposition
12/23/02	Miles v. Philip Morris – deposition
2/6/03	Miles v. Philip Morris - Trial
5/16/03 and 6/27/03	Tolbert v. Monsanto - deposition
5/12/03	Turner v. RJ Reynolds - deposition
6/30/03	Krutsinger v Monsanto - deposition
3/12/04	Krutsinger v Monsanto - deposition
12/22/04	King v. BNSF - deposition
6/13/05	Palazzo v. Amtrak - deposition
6/17/05	Schwab v. Philip Morris, et al. -deposition
7/15/05	Krustinger v. Monsanto - Trial
2/22/06	Allgood v General Motors - deposition

CURRICULUM VITAE

Name: Peter G. Shields, M.D. Date Prepared: March 23, 2006

Professor of Medicine and Oncology
Associate Director for Cancer Control and Population Sciences
Director, Cancer Genetics and Epidemiology
Lombardi Cancer Center
Georgetown University Medical Center
3800 Reservoir Rd. NW
LL (s) Level, Room 150, Box 571465
Washington, DC 20057-1465
Tel: 202-687-0003
Fax: 202-687-0004
EMAIL: pgs2@georgetown.edu

Education:

- 1979 Bachelor of Arts (Biochemistry and American Civilization), University of Pennsylvania, Philadelphia, PA
- 1983 Medical Doctor, Mount Sinai School of Medicine, New York, NY
- 1983 Internship, Internal Medicine, The George Washington University Hospital, Washington, DC
- 1984 Residency, Internal Medicine, The George Washington University Hospital, Washington, DC
- 1987 Clinical Fellowship, Hematology and Oncology, The George Washington University Hospital, Washington, DC
- 1988 Fellow-Intramural Research Training Award (IRTA), National Institutes of Health, National Cancer Institute, Division of Chemical Etiology, Laboratory of Human Carcinogenesis, Bethesda, MD
- 1990 Summer Program in Epidemiology, Johns Hopkins Univ., School of Public Health and Hygiene, Baltimore, MD (Graduate course work in epidemiology and risk assessment)
- 1992 Summer Program in Epidemiology, Johns Hopkins Univ., School of Public Health and Hygiene, Baltimore, MD (Graduate course work in statistics)

Brief Chronology of Employment:

- 1984 - 1996 Medical Director, La Clinica del Pueblo, Washington, DC
- 1985 - 1987 Intensivist, Capitol Hill Hospital, Washington, DC
- 1986 - 1987 Emergency Medicine Physician, Capitol Hill Hospital, Washington, DC
- 1986 - 1987 Senior Clinical Associate, Washington Occupational Health Associates, Inc., Washington, DC
- 1990 - 1999 Commissioned Officer: United States Public Health Service. Highest rank achieved - Captain (CO-06)
- 1990 - 1995 Senior Clinical Investigator, National Institutes of Health, National Cancer Institute, Division of Cancer Etiology, Laboratory of Human Carcinogenesis, Bethesda, MD
- 1995 - 1997 Acting Section Chief, National Institutes of Health, National Cancer Institute, Division of Basic Sciences, Laboratory of Human Carcinogenesis, Molecular Epidemiology Section, Bethesda, MD

1997 - 1999	Section Chief, National Institutes of Health, National Cancer Institute, Division of Basic Sciences, Laboratory of Human Carcinogenesis, Molecular Epidemiology Section, Bethesda, MD
1997-2005	Chairperson, Board of Directors. La Clinica del Pueblo, Inc.Washington, DC
2000-Date	Special Volunteer, Laboratory of Human Carcinogenesis, Division of Basic Sciences, National Cancer Institute, Bethesda, MD
2000-Date	Professor of Medicine and Oncology, Georgetown University Medical Center, Washington, DC (Tenure granted 2003)
2000-Date	Director, Division of Cancer Genetics and Epidemiology Program, Department of Oncology, Georgetown University Medical Center, Washington, DC
2000-Date	Leader, Cancer Genetics and Epidemiology Program, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC
2000-Date	Associate Director for Cancer Control and Population Sciences, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC
2005-Date	Member, Board of Directors. La Clinica del Pueblo, Inc. Washington, DC
2006-Date	Senior Medical Director, Capital Breast Care Center, Washington, DC

Board Certification and Eligibility:

1984 – Diplomate, National Board of Medical Examiners
1986 – Diplomate, American Board of Internal Medicine
1989 – Diplomate, American Board of Internal Medicine Subspecialty–Oncology
1990 – Diplomate, American Board of Internal Medicine Subspecialty–Hematology (exp 12/31/2000)

Academic Appointments:

1986 - 1990	Clinical Instructor--Department of Medicine, The George Washington University Medical Center, Washington, DC
1990 - 1997	Assistant Professor of Medicine--Division of Hematology and Oncology, The George Washington University Medical Center, Washington, DC
1992 - 1996	Board of Directors--Metropolitan Capitol College of Occupational and Environmental Medicine
1997 - 1999	Associate Professor of Medicine--Division of Hematology and Oncology, The George Washington University Medical Center, Washington, DC
1997 - 1999	Tenured Investigator, National Institutes of Health, National Cancer Institute, Division of Basic Sciences, Laboratory of Human Carcinogenesis, Molecular Epidemiology Section, Bethesda, MD
2000-Date	Professor, Departments of Oncology and Medicine, Georgetown University Medical Center, Washington, DC
2004-Date	Professor, Department of Pediatrics and Child Health, Howard University, Washington, DC

Societies:

Society for Research on Nicotine and Tobacco
American Association of Cancer Research (Molecular Epidemiology Group)
American College of Occupational and Environmental Medicine

American Conference of Governmental Industrial Hygienists
American Society of Preventive Oncology
Medical Society of the District of Columbia
Metropolitan Capital College of Occupational and Environmental Medicine

Honors and Other Special Scientific Recognition

Departmental Honors, Department of American Civilization, University of Pennsylvania, 1979
Departmental Honors, Department of Biochemistry, University of Pennsylvania, 1979
Magna Cum Laude, University of Pennsylvania, 1979
Alpha Omega Alpha Honor Society, Mount Sinai School of Medicine, 1982
Physician Recognition Award, American Medical Association, 1990
Distinguished Service Medal, George Washington University Medical Center, 1993
Janice Jirau Award for Community Service, Comprehensive AIDS Resources and Education Consortium, 1994
Physician Recognition Award, American Medical Association, 1994
Steering Committee Chairman, elected position. Molecular Epidemiology Group, American Association for Cancer Research, 2000-2001

Grants Received – Expired

U.S. Army Medical Research Acquisition, Department of the Army
Title: Environmental Exposure, Genetic Polymorphisms, and p53 Mutational Spectra in a Case-Control Study of Breast Cancer. — 1994-1997 — $486,000 (total)
Role on Project: Principal Investigator

This project focused on the detection of p53 mutations in relation to genetic polymorphisms for breast cancer risk with collaborators at the University of Buffalo.

Office of Special Populations Research
Title: NCI and Howard University Training Program for Molecular Epidemiology. — 1998-2000 — $200,000 (total)
Role on Project: Principal Investigator

This project was to provide multidisciplinary training to minority researchers to advance careers in molecular epidemiology.

Office of Special Populations Research, NCI
Title: Cellular Responses to Mutagens in Lung Cancer Cases and Controls — 1998-2000 — $195,000 (total)
Role on Project: Co-Investigator

This project investigates the relation of mutagen sensitivity and genetic polymorphisms in lung cancer risk.

Office of Special Populations Research
Title: Gene-environment interactions for breast cancer risk and survival in different racial and ethnic groups. — 1999-2000 10% — $138,000 (total)

Role on Project: Principal Investigator

This project is a collaborative effort with investigators at the MD Anderson Cancer Center to study the effort of genetic polymorphisms and modification of exposures that leads to cancer risk and survival.

Komen Foundation
Title: Georgetown University and Howard University Medical Center Training Program for Molecular Epidemiology — 2000-2001, $186,000 (total)
Role on Project: Principal Investigator

This project recruits and trains pre- and postdoctoral fellows to study racial differences in cancer risk and methods to study minority populations.

NCI, P50 CA58185-09 (Dickson, PI)
Title: Specialized Program of Research Excellence in Breast Cancer — 09/00 - 08//01, $1,303,132 (annual)
Role on Project: PI of Biomarker Core resource; PI of pilot project

To collect patient histories and biological fluids to be used by investigators in the study of breast cancer risk factors and outcomes.

Park Foundation
Title: Molecular Epidemiology of Secondary Lung Cancer — 2000-2002
Role on Project: Principal Investigator — $200,000 (total)

To determine p53 mutational spectra and genetic susceptibility in breast tumors and secondary lung cancers in Swedish women treated with radiation therapy.

Department of the Army, DAMD BC980583 — 10/99-9/03
Title: Molecular epidemiology of breast cancer: Development & Validation of Acetylation Methods for Carcinogen-DNA Adduct Detection — $316,782 (total directs)
Role on Project: Principal Investigator

This is an Idea Grant to develop and apply carcinogen DNA adduct detection methods using ^{14}C-acetic anhydride postlabeling in normal breast tissues, liver and blood.

NCI, 5 U24 CA78146-03 (Isaacs, PI)
Title: Cancer Genetics Network — 09/99-09/04
Role on Project: Co-Principal Investigator

To participate in accrual of cancer cases with and without a family history of cancer.

NCI P20 CA91403 (Shields)
Title: University of District of Columbia and Lombardi Cancer Center Partnership for Cancer Research training, education and outreach. — 2001-2004, $63,636 (annual directs)
Role on Project: Principal Investigator

To develop a joint training program for UDC faculty and undergraduates in the area of cancer research and education.

NCI, P30 CA51008-11S1 – Supplement (Pestell, PI)
Office of Special Populations Research
Title: Georgetown University and Howard University Training Program for Molecular Epidemiology. — 2000-2003, $125,000 (annual)
Role on Project: Principal Investigator of supplement

This project is to provide multidisciplinary training to minority researchers to advance careers in molecular epidemiology.

NIH, 1 P50 CA84718-01 (Lerman, PI)
Title: Transdisciplinary Tobacco Use Research Center — 10/99-9/04
Role on Project: Co-Principal Investigator; Site PI — $1,500,000 (annual)

This Tobacco Center is similar to a program project. Dr. Shields is Co-PI of the entire center and PI of a project that studies genetic determinants of smoking topography and smoking behavior determinants on carcinogen adduct formation. Dr. Shields also is the PI of the molecular genetics core.

<u>Grants Received – Current</u>

NCI, P30 CA51008-11S1 (Dritchillo, PI)
Title: Lombardi Comprehensive Center Core Grant — 1996-2008
Role on Project: Associated Director for Cancer Control and Population Sciences; Program Director of Cancer Genetics and Epidemiology Program

To provide a coordinated and comprehensive cancer research program.

National Cancer Institute R01 (Freudenheim, PI)
Title: Methylation and Oxidation in Breast Cancer Epidemiology — 2002-2007, $1,700,00 (total directs)
Role on Project: Co-Principal Investigator, Site PI

To determine the nutritional and genetic risk factors for p53 mutations and hypermethylation of genes involved in breast cancer

National Cancer Institute R01 (Shields, PI)
Title: Molecular Epidemiology of Secondary Lung Cancer — 2002-2007
Role on Project: Principal Investigator — $2,503,634 (total directs)

To determine p53 mutational spectra and genetic susceptibility in breast tumors and secondary lung cancers in Swedish women treated with radiation therapy.

Department of the Army, Breast Center of Excellence (Shields, PI) — 01/01/03-12/31/07
Title: Molecular Epidemiology and Breast Carcinogenesis: — $5,000,000 (total directs)

Alcohol Drinking as a Paradigm
Role on Project: Principal Investigator

This is a multidisciplinary, multiple project Center that will study the causes of breast cancer as it relates to alcohol drinking and diet. The projects include cell culture, animal and human studies, including 3 that are epidemiology.

NCI Minority Serving Institution/Comprehensive Cancer Center Partnership – U56 (Shields, PI) 01/01/03 - 12/31/08
Title: University of the District of Columbia and the Lombardi Cancer Center Partnership for Cancer Prevention and Control $368,721 (total directs)
Role on Project: Principal Investigator

This is a multiproject grant to develop new research projects in the areas of cancer prevention and control that are based in the African American Community. It also includes an undergraduate and masters level training program.

Avon Foundation-American Association of Cancer Research
Title: Avon Foundation-AACR International Scholars Program
Role on Project: Principal Investigator

This is a training program that allows researchers from lesser developed countries to learn molecular epidemiology.

External Committees and Service

1993 - 1999	Member, Biochemical Epidemiology Committee, NCI. Serves to review and approve research protocols for the Division of Cancer Epidemiology and Genetics.
1994 - 1996	Howard Hughes Medical Institute, NCI Research Scholars Advisor
1996 - 1998	Member, Contract Utilization Committee, NCI. Serves to review the contract portfolio for the Division of Cancer Epidemiology and Genetics.
1997 - 1998	Member, NCI Task Force for Breast Cancer. Task force to review current research agenda for the NCI.
1997	Program Peer Reviewer, American Cancer Society, to review ACS intramural epidemiology program, Atlanta, GA
1997	Grant Review Committee, Department of Energy, to review DOE grant proposals from program entitled Radiation Health Effects in the Russian Federation, Arlington, VA
1998	Program Committee member – International Conference of Carcinogenesis and Risk Assessment, Austin, TX
1998	Program committee member – IV International Conference on Cancer, Venice, Italy 1997 Molecular Epidemiology Coordinating Committee, NCI. Committee selected by the Director, NCI, to define an intramural research agenda for molecular epidemiology.
1997 - 1999	Member, Biorepository Committee, NCI, to oversee biorepository, serves at Frederick, MD
1998 - 1999	Reviewer, Epidemiology and Disease Control Study Section 2, NIH, Bethesda, MD (Ad Hoc Reviewer)

1998	Program Committee – Carcinogenesis, Metabolism, Mutagenesis and DNA Repair Chairperson. AACR 1999 Annual Meeting,
1998	Member, Tobacco Research Implementation Group, NCI, Bethesda, MD
1998-Date	Member, Joint Coordinating Committee for Radiation Effects Research in the Russian Federation. Department of Energy
1999-Date	Member, Epidemiology and Disease Control Study Section 2, NIH, Bethesda, MD
1997-2002	Molecular Epidemiology Group – Newly formed working group of molecular epidemiologists within the AACR. Dr. Shields served on the steering committee as the Communications Committee Chairperson 1999, and elected Steering Committee Chairperson 2000
1999-2001	Member, Institute of Medicine Committee on "Assessing the science base for tobacco harm reduction"
2001-Date	Member, District of Columbia Board of Medicine
2001	Program Committee, Chair of Genetic Epidemiology. American Association of Cancer Research Annual Meeting for 2002
2001-Date	Member, P01 Advisory Board. Barbara Weber, PI. University of Pennsylvania, Phila., PA
2002	Reviewer, MD Anderson Cancer Center Prevention Program. Houston, TX
2002 - Date	Member, Genitourinary Spore Grant Advisory Board (PI: C. Dinney), Houston Texas
2002 - Date	Member, Scientific Advisory Committee, State of Massachusetts Tobacco Control Program
2003 - Date	Chair, Steering Committee, Howard/Hopkins Cancer Center Partnership, Washintgon, DC
2004-Date	Member, Subcommittee A- Cancer Centers, Initial Review Group, National Cancer Institute, National Institutes of Health
2004-Date	Chair, Steering Committee, Roswell Park Cancer Center/University of Puerto Rico Partnerhip, Buffalo, NY
2005 - 2006	Member, Local Liason Committee, American Association of Cancer Research
2005 - Date	Member, AACR Task Force on Behavioral Science and Cancer
2005 - Date	Chair, Molecular Epidemiology Interest Group. American Society of Preventive Oncology
2005- Date	Member, Executive Committee. American Society of Preventive Oncology
2006-Date	Member, Scientific Review Panel. Cancer Research and Prevention Foundation

University Service

2000-Date	Executive Committee, Tumor Biology Program. Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC
2000-2001	Chairperson, Head of Biostatistics Unit Search Committee, Lombardi Cancer Center, Washington, D.C.
2000-Date	Executive Committee Member, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC
2000-2003	M..D.- Ph.D. Executive Committee, Georgetown University Medical Center Washington, DC
2000-Date	Member, Executive Committee Georgetown University Tumor Biology Committee
2002-2003	Member, Georgetown University Public Health Task Force
2005-Date	Member, Georgetown University Rank and Tenure Promotions Committee

Peer-Reviewed Journal Activities

1996-1999	Advisory Editorial Board for Cancer Epidemiology, Biomarkers and Prevention
1999-2002	Member, Editorial Board, Carcinogenesis
1997-1999	Editorial Board for Oncology Reports
1999-2002	Associate Editor for Cancer Epidemiology, Biomarkers and Prevention
1998-2003	Advisory Editorial Board for Pharmacogenetics
2002-Date	Section Editor for Cancer Epidemiology, Biomarkers and Prevention
2003-Date	Associate Editor for International Journal of Cancer Prevention
2005-Date	Associate Editor for Molecular Carcinogenesis

Reviewer - Journal of the American Medical Association, Journal of the National Cancer Institute, Cancer Research, Mutation Research, Carcinogenesis, International Journal of Cancer, Biotechniques, Journal of Clinical Pathology, Environmental Sciences and Technology, Cancer Genetics and Cytogenetics, Biological Psychiatry, Cancer, Annals of Internal Medicine, Lancet, Breast Cancer Research and Treatment and others.

Thesis Advisory Activities

Tracy Ford, Masters in Genetics, CYP1A1 and Breast Cancer Risk. Howard University. Degree Awarded, 1996.

Lea Harty, Ph.D. in Epidemiology, ADH3 Genetic Polymorphisms in Oral Cavity Cancer. Johns Hopkins University. Degree Awarded, 1997.

Bryan Cobb, Masters in Genetics. NAT1 in Prostate Cancer. Howard University Hospital. Degree Awarded, 1997.

Tosin Foseru, Masters in Public Health. P53 Mutations in Human cancer. George Washington University. Degree Awarded, 1997.

Edwin Park, Masters in Public Health. PCBs in Breast Tissues, George Washington University. Degree Awarded, 1998.

Tasha Barnes, Masters in Genetics. NAT2 in Prostate Cancer. Howard University. Degree Awarded, 1998.

Dawn Elder, Masters in Genetics. CYP1A1 and GSTM1 in Oral Cavity Haman. Howard University. Degree Awarded, 1998.

Kareem Washington, Masters in Genetics. Micropreparative techniques for DNA-adduct purification. Howard University. Degree Awarded 2000.

Simone Sumner. Ph.D. candidate, Genetics Department, Howard University. Molecular Markers and Epidemiology of Breast Cancer. Degree awarded. 2004.

Ramona Dumitrescu. Ph.D. candidate, Universitatea Babes-Bolyai, ClujNapoca, Romania. Genotypic and Phenotypic Correlations in Breast Normal Tissues. Degree awarded. 2004.

Meredith Tennis. Ph.D candidate, Tumor Biology Program, Georgetown University. Molecular Epidemiology of Secondary Lung Cancers. Degree pending.

Luisel Ruiz. Ph.D. candidate, Tumor Biology Program, Georgetown University. Identification of low penetrance breast cancer risk genes affecting risk in women with BRCA1 mutations. Degree pending.

Adana Llanos. Ph.D. candidate,Genetics Department, Howard University. Mammographic breast density and breast cancer risk. Degree pending.

Teaching Activities

2000-Date Executive Committee and faculty member. Tumor Biology Program. Lombardi Cancer Center. Georgetown University Medical Center, Washington, DC

2000-Date Executive Committee and faculty member. M.D./Ph.D. Training Program. Georgetown University Medical Center, Washington, DC

2000-2004 Course Director. Topics in Molecular Epidemiology. Tumor Biology Program, Lombardi Cancer Center. Georgetown University Medical Center, Washington, DC

2000-Date Guest Lecturer in various courses in Georgetown Tumor Biology Training Program and Medical School, Howard University Department of Genetics, University of District of Columbia.

2004-Date Co-course director. Cancer Prevention and Control. Lombardi Cancer Center. Georgetown University Medical Center, Washington, DC

Research Interests:

1. Mechanisms of chemical carcinogenesis; inherited susceptibilities, metabolism of carcinogens, DNA damage, DNA repair and cell cycle control.

2. Molecular epidemiology; uses in risk assessment, development and application of new non-invasive techniques for exposure monitoring; inherited predispositions to cancer

BIBLIOGRAPHY

Dr. Peter G. Shields

Peer-Reviewed Papers

2006- **Shields, P. G.** and Chase, K. C.: Torsion of the omentum: another vibration-related injury. J. Occup. Med. 30: 892-894, 1988.

2007- **Shields, P.G.**, Dawkins, F., Holmlund, J., Cohen, P. and Schulof, R. S.: Low-dose multidrug chemotherapy plus pneumocystis prophylaxis for HIV-related Kaposi's sarcoma. J. AIDS 3: 695-700, 1990.

3. **Shields, P.G.**, Povey, A. C., Wilson, V., Weston, A. and Harris, C. C.: Combined high performance liquid chromatography/^{32}P-postlabeling assay of N^{7}methyldeoxyguanosine in human lung. Cancer Res. 50: 6580-6584, 1990.

4. **Shields, P.G.**, Sugimura, H., Caporaso, N. E., Petruzzelli, S. F., Bowman, E. D., Trump, B. F., Weston, A. and Harris, C. C.: Polycyclic aromatic hydrocarbon-DNA adducts and the CYP1A1 RFLP. Environ. Health Perspect. 98: 191-194, 1992.

5. Caporaso, N. E., **Shields, P.G.**, Landi, M. T., Shaw, G. L., Tucker, M. A., Hoover, R., Sugimura, H., Weston, A. and Harris, C. C.: The epidemiologic and laboratory implications of non-correspondence between the debrisoquine metabolic phenotype and DNA-based assays: Implications of misclassification for the association of lung cancer and the debrisoquine metabolic phenotype. Environ. Health Perspect, 98: 101-105, 1992.

6. Qu, Y. H., Xu, G. X., Zhou, J. Z., Chen, T. D., Zhun, L. F., **Shields, P.G.**, Wong, H. W., and Gao, Y. T.: Genotoxicity of heated cooking oil vapors. Mutation Research, 298: 105-111, 1992.

7. Kato, S., **Shields, P.G.**, Caporaso, N. E., Hoover, R., Weston, A. and Harris, C. C.: CYP2E1 polymorphism and racial variation. Cancer Res. 52: 6712-6715, 1992.

8. Weston, A., Bowman, E. D., **Shields, P.G.**, Trivers, G. E., Poirier, M. D., Santella, R. M. and Manchester, D. K.: Detection of polycyclic aromatic hydrocarbon-DNA adducts in human lung. Environ. Health Perspect. 90: 257-259, 1993.

9. **Shields, P.G.**, Harris, C. C., Petruzzelli, S., Bowman, E. D. and Weston, A.: Standardization of the ^{32}P-postlabeling assay for polycyclic aromatic hydrocarbon - DNA adducts. Mutagenesis, 8: 121-126, 1993.

10. Kato, S., Petruzzelli, S., Bowman, E. D., Turteltaub, K. W.,Weston, A. and **Shields, P.G.**: 7-alkyl-deoxyguanosine adduct detection by two step high performance liquid chromatography and the ^{32}P-postlabeling assay. Carcinogenesis, 14: 545-550, 1993.

11. Pfeifer, A. M. A., Cole, K. E., Smoot, D. T., Weston, A., Groopman, J. D., **Shields, P.G.**, Vignaud, J. M., Juillerat, M., Lipsky, M. M., Trump, B. F., Lechner, J. F., and Harris, C. C.: SV40 T-antigen immortalized normal human liver epithelial cells express hepatocyte characteristics and metabolize chemical carcinogens. Proc. Natl. Acad. Sci. USA, 90: 5123-5127, 1993.

12. Wilson, V. L., Taffe, B. G., **Shields, P.G.**, Povey, A. C. and Harris, C. C.: Detection and quantitation of 8-hydroxydeoxyguanosine adducts in peripheral blood of people exposed to ionizing radiation. Environ. Health Perspect, 99: 261-263, 1993.

13. **Shields, P.G.**, Caporaso, N. E., Falk, R. T., Sugimura, H., Trivers, G. E., Trump, B. F., Hoover, R. N., Weston, A. and Harris, C. C.: Lung cancer, race and a CYP1A1 genetic polymorphism. Cancer Epidemiology, Biomarkers and Prevention, 2: 481-485, 1993.

14. **Shields, P.G.**, Bowman, E. D., Harrington, A. M., Doan, V. T. and Weston, A.: Polycyclic aromatic hydrocarbon DNA adducts in human lung and cancer susceptibility genes. Cancer Res., 53: 3486-3492, 1993.

15. Vineis, P., Bartsch, H., Caporaso, N. E., Kadlubar, F. F., Landi, M. T., Malaveille, C., **Shields, P.G.**, Skipper, P., Talaska, G., Tannenbaum, S. P.: Genetically-based N-acetyltransferase metabolic polymorphism and low level environmental exposure to carcinogens. Nature, 369: 154-156, 1994.

16. Kato, S., **Shields, P.G.**, Caporaso, N. E., Sugimura, H., Trivers, G. E., Tucker, M. A., Trump, B. F., Weston, A. and Harris, C. C.: Analysis of cytochrome P4502E1 genetic polymorphisms in relation to human cancer. Cancer Epidemiology, Biomarkers and Prevention 3: 457-526, 1994.

17. Landi, M. T., Bertazzi, P. A., Clark, G., Lucier, G. W., Garte, S. J., Cosma, G., **Shields, P.G.**, Whitehouse, J. and Caporaso, N. E.: Association between CYP1A1 genotype, mRNA expression and enzymatic activity in humans. Pharmacogenetics 4: 242-246, 1994.

18. **Shields, P.G.**, McCunney, R., and Chase, K. H.: Confined space hazards: Combined exposure to styrene, fiberglass and silica. J. Occup. Med. 37: 180-185, 1995.

19. Kato, S., Onda, M., Matsukura, N., Tokunaga, A., Tajiri, T., Kim, D. Y., Tsuruta, H., Matsuda, N., Yamashita, K. and **Shields, P.G.**: Genetic and environmental risk factors for the gastric cancer. In Nishi, M., Sugano, H. and Takahashi, T (Eds.): 1st Gastric Cancer Congress. Monduzzi Editore S.p.A., Bologna, 1995, 385-389.

20. Kato, S., Onda, M., Matsukura, N., Tokunaga, A., Tajiri, T., Kim, D. Y., Tsuruta, H., Matsuda, N., Yamashita, K. and **Shields, P.G.**: Cytochrome P4502E1 (CYP2E1) genetic polymorphism in case-control study of gastric cancer and liver disease. Pharmacogenetics, 5: 5141-5144, 1995.

21. **Shields, P.G.**, Xu, G. X., Blot, W., Trivers, G., Weston, A., Qu, Y. H., and Harris, C. C.: Aldehyde generation and genotoxicity from heated Chinese and United States Cooking Oils. J. Natl. Cancer Inst. 87: 836-841, 1995.

22. Kato, S., Bowman, E. D., Blomeke, B. and **Shields, P.G.** Human lung carcinogen DNA adduct levels mediated by genetic polymorphisms in vivo. J. Natl. Cancer Inst. 87: 902-907, 1995.

23. Ambrosone, C. B., Freudenheim, J. L., Graham, J. R., Marshall, J. R., Vena, J. E., Brasure, J. R., Laughlin, R., Nemoto, T., Michalek, A. M., Harrington, A., Ford, T. D. and **Shields, P.G.**: Cytochrome P4501A1 and glutathione S-transferase (M1) genetic

polymorphisms and postmenopausal breast cancer risk. Cancer Res., 55: 3483-3485, 1995.

24. Pellizzari, E. D., Michael, L. C., Thomas, K. W., **Shields, P.G.** and Harris, C.: Identification of 1,3-butadiene, benzene, and other volatile organics from wok oil emissions. J. Expos. Anal. Environ. Epidemiol., 5: 77-87, 1995.

25. Rothman, N., **Shields, P.G.**, Poirier, M. C., Harrington, A. M., Ford, D. P. and Strickland, P. T.: The impact of glutathione *s*-transferase M1 and cytochrome P450 1A1 genotypes on white-blood-cell polycyclic aromatic hydrocarbon-DNA adduct levels in humans. Mol. Carcinog., 14: 63-68, 1995.

26. Shinmura, K., Sugimura, H., Naito, Y., **Shields, P.G.** and Kino, I.: Frequent co-occurrence of mutator phenotype in synchronous, independent multiple cancers of the stomach. Carcinogenesis, 16: 2989-2993, 1995.

27. Ambrosone, C. B., Freudenheim, J. L., Marshall, J. R., Graham, S., Vena, J. E., Brasure, J. R., Michalek, A. M., Laughlin, R., Nemoto, T. and **Shields, P.G.** The association of polymorphic N-acetyltransferase (NAT2) with breast cancer risk. Ann N.Y.Acad.Sci, 768: 250-252, 1995.

28. Blomeke, B., Greenblatt, M.J., Doan, V. D., Bowman, E. D. Murphy, S. E., Chen, C. C., Kato, S. and **Shields, P.G.**: Distribution of 7-alkyl-2'-deoxyguanosine adduct levels in human lung. Carcinogenesis, 17: 741-748, 1996.

29. Kato, S., Onda, M., Matsukura, N., Tokunaga, A., Matsuda, N., Yamashita, K. and **Shields, P.G.** Genetic polymorphisms of the cancer related gene and Helicobacter pylori infection in Japanese gastric cancer patients. An age and gender matched case-control study. Cancer, 77: 1654-1661, 1996.

30. **Shields, P.G.**, Ambrosone, C. B., Bowman, E. D., Harrington, A. M., Graham, S., Marshall, J. R., Vena, J. E., Laughlin, R., Nemoto, T., and Freduenheim, J. L.: A cytochrome P450IIE1 genetic polymorphism (CYP2E1) and tobacco smoking in breast cancer. Mol. Carcinog., 17: 144-150, 1996.

31. Ambrosone, C. B., Freudenheim, J. L., Marshall, J. R., Graham, S., Vena, J. E., Brasure, J. R., Michalek, A. M., Bowman, E. D., Gillenwater, K., Harrington, A. M. and **Shields, P.G.**: N-Acetyltransferase (NAT2), Cigarette smoking and breast cancer risk. J. Am. Med. Assoc., 276: 1494-1501, 1996.

32. Ambrosone, C. B., Kato, S., Bowman, E. D., Harrington, A. M., Blomeke, B., Freudenheim, J. L., Graham, S., Marshall, J. R., Vena, J. E., Brasure, J. R. and **Shields, P.G.**: Chemicals and Cancer. Euro. J. Cancer Prev., 5: 25-27, 1996.

33. Landi, M. T., Zocchetti, C., Bernucci, I., Kadlubar, F. F., Tannenbaum, S., Skipper, P., Bartsch, H., Malaveille, C., **Shields, P. G.,** Caporaso, N. E. and Vineis, P.: Cytochrome P4501A2: enzyme induction and genetic control in determining 4-aminobiphenyl-hemoglobin adduct levels. Cancer Epidemiology, Biomarkers and Prevention, 5: 693-698, 1996.

34. Blomeke, B., Bennett, W. P., Harris, C. C. and **Shields, P.G.**: Serum, plasma and paraffin-embedded tissues as sources of DNA for studying cancer susceptibility genes. Carcinogenesis, 18: 1271-1275, 1997.

35. Kato, S., Onda, M.., Matsukura, N., Tokunaga, A., Matsuda, N., Yamashita, K., **Shields, P.G.**: Helicobacter pylori infection and genetic polymorphisms for cancer-related genes in gastric carcinogenesis. Biomed & Pharmacother, 51: 145-149, 1997.

36. Bowman, E. D., **Shields, P.G.**, Caporaso, N. E., Tucker, M. A., Hoover, R. N., Trump, B. F. and Harris, C. C.: Chromosome 13 poly(ADP-ribose) polymerase polymorphisms and lung cancer risk. Oncol. Rpt. 4: 269-272, 1997.

37. Harty, L. C., Caporaso, N. E., Hayes, R. B., Winn, D. M., Bravo, E., Blot, W. J., Kleinman, D. V., Brown, L. M., Armenian, H. K., Fraumeni, J. F. and **Shields, P.G.**: Susceptibility to oral cavity cancer associated with the alcohol dehydrogenase type 3 gene. J. Natl. Cancer Inst. 89: 1698-1705, 1997.

38. Lerman, C., Caporaso, N., Main, D., Audrain, J., Boyd, N. R., Bowman, E. D. and **Shields, P.G.**: Depression and self-medication with nicotine: the modifying influence of the dopamine D4 receptor gene. Health Psychology, 17: 56-62, 1998.

39. Lerman, C., **Shields, P.G.**, Main, D., Audrain, J., Roth, J., Boyd, N. R. and Caporaso, N. E.: Lack of association of tyrosine hydroxylase genetic polymorphism with cigarette smoking. Pharmacogenetics. 7: 521-524, 1998.

40. Bowman, E. D., Blomeke, B., Lensing, W., **Shields, P.G.**: Apolipoprotein E allelic frequency in elderly smokers. Amer. J. Med. Genet. 76: 32-36, 1998.

41. Ambs, S., Merriam, W. G., Bennett, W. P., Felley-Bosco, E., Ogunfusika, M. O., Oser, S. M., Klein, S., **Shields, P.G.**, Billiar, T. R., and Harris, C. C.: Frequent nitric oxide synthase-2 expression in human colon adenomas: implication for tumor angiogenesis and colon cancer progression. Cancer Res. 58: 334-341, 1998.

42. Ambrosone, C. B., Freudenheim, J. L., Sinha, R., Graham, S., Marshall, J. R., Vena, J. E., Laughlin, R., Nemoto, T. and **Shields, P.G.**: Breast cancer risk, meat consumption and N-acetyltransferase (NAT2) genetic polymorphisms. Int. J. Cancer, 75: 825-830, 1998.

43. Moysich, K. B., Ambrosone, C. B., Vena, J. E., **Shields, P.G.**, Mendola, P., Kostyniak, P., Greizerstein, H., Graham, S., Marshall, J. R. Schisterman, E. F. and Freudenheim, J. L.: Environmental organochlorine exposure and postmenopausal breast cancer risk. Cancer Epidemiol. Biomarkers and Prev. 7: 181-188, 1998.

44. Lerman, C., **Shields, P.G.**, Audrain, J., Main, D., Cobb, B., Boyd, N. R. and Caporaso, N.: The role of the serotonin transporter gene in cigarette smoking. Cancer Epidemiol. Biomarkers Prev., 7: 253-255, 1998.

45. Thompson, P. A., **Shields, P.G.**, Freudenheim, J. L., Stone, A., Vena, J. E., Marshall, J. R., Graham, S., Laughlin, R., Nemoto, T., Kadlubar, F. F. and Ambrosone, C. B.: Genetic polymorphisms in catechol-O-methyltransferase, menopausal status, and breast cancer risk. Cancer Res., 58: 2107-2110, 1998.

46. **Shields, P.G.**, Lerman, C., Audrain, J., Bowman, E. D., Main, D., Boyd, N. R. and Caporaso, N. E.: Dopamine D4 receptors and the risk of cigarette smoking in African-Americans and Caucasians. Cancer Epidemiol. Biomarkers Prev., 7: 453-458, 1998.

47. Mace, K., Bowman, E. D., Vautravers, P., **Shields, P.G.**, Harris, C. C. and Pfeifer, A. M. A.: Characterization of xenobiotic-metabolizing enzyme expression in human bronchial mucosa and peripheral lung tissues. Eur. J. Cancer. 34: 914-920, 1998.

48. Przygodzki, R. M., Bennett, W. P., Guinee, D. G., Jr., Khan, M. A., Freedman, A., **Shields, P.G.**, Travis, W. D., Jett, J. R., Tazelaar, H., Pairolero, P., Trastek, V., Liotta, L. A., Harris, C. C. and Caporaso, N. E.: p53 mutation spectrum in relation to GSTM1, CYP1A1, and CYP2E1, in surgically treated patients with non-small cell lung cancer. Pharmacogenetics. 8: 503-11, 1999.

49. Menola, P., Moysich, K. B., Freudenheim, J. L., **Shields, P.G.**, Schisterman, E. F., Graham, S., Marshall, J. R., Vena, J. E. and Ambrosone, C. B.: Risk of recurrent spontaneous abortion, cigarette smoking, and genetic polymorphisms in NAT2 and GSTM1. Epidemiology. 9: 666-668, 1998.

50. Lerman, C., Caporaso, N. E., Main, D., Audrain, J., Bowman, E. D., Lockshin, B., Boyd, N. R., **Shields, P.G.**: Association of dopamine transporter (DAT1) and DRD2 receptor genes with cigarette smoking. Health Psychology., 18: 14-20, 1999.

51. Ambs, S., Bennett, P. M., Merriam, W. G., Ogunfusika, M.O., Oser, S. M., Harrington, A. M., **Shields, P.G.**, Felley-Bosco, E., Hussain, S. P., Harris, C. C.: Relationship Between p53 Mutations and Inducible Nitric Oxide Synthase Expression in Human Colorectal Cancer. J. Natl. Cancer Inst. 91: 86-88, 1999.

52. Ambrosone, C. B., Freudenheim, J. L., Thompson, P. A., Bowman, E., Vena, J. E., Marshall, J. R., Graham, S., Laughlin, R., Nemoto, T. and **Shields, P.G.**: Manganese superoxide dismutase (SOD2) genetic polymorphisms, dietary antioxidants and risk of breast cancer. Cancer Research. 59: 602-606, 1999.

53. Ambrosone, C. B., Coles, B. F., Freudenheim, J.L., and **Shields, P. G.**: Glutathione-S-transferase (GSTM1) genetic polymorphisms do not affect human breast cancer risk, regardless of dietary antioxidants. J. Nutr. 129: 565-8, 1999.

54. Moysich, K. B., **Shields, P.G.**, Freudenheim, J. L., Schisterman, E. F., Vena, J. E., Kostyniak, P., Greizerstien, H., Marshall, J. R., Graham, S., and Ambrosone, C. B.: Polychlorinated biphenyls, cytochrome p4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev. 8: 41-4, 1999.

55. Moysich, K. B., Mendola, P., Schisterman, E. F., Freudenheim, J. L., Ambrosone, C. B., Vena, J. E., **Shields, P.G.**, Koystyniak, P., Greizerstein, H., Graham, S., and Marshall, J. R.: An evaluation of proposed frameworks for grouping polychlorinated biphenyl (PCB) congener data into meaningful analytic units. Am J Ind Med 35: 223-31, 1999.

56. Rusin, M., Butkiewicz, D., Malusecka, E., Zborek, A., Harasim, J., Czyzewski, K., Bennett, W. P., **Shields, P.G.**, Weston, A., Welsh, J. A., Krzyzowska-Gruca, S., Chorazy, M. and Harris, C. C.: Molecular epidemiological study of non-small-cell lung

cancer from an environmentally polluted region of Poland. Brit. J. Cancer, 80: 1445-1452, 1999.

57. Lehman, T.A., Haffy, B.G., Carbone, C.J., Bishop, L.R., Gumbs, A.A., Krishnan, S., **Shields, P.G.**, Modali, R., Turner, B.C.: Elevated Frequency and Functional Activity of a Specific Germ-Line p53 Intron Mutation in Familial Breast Cancer. Cancer Research, 60: 1062-1069, 2000.

58. Harty, L. C., **Shields, P.G.**, Winn, D. M., Caporaso, N. E. and Hayes, R. B.: Self-collection of oral epithelial cell DNA under instruction from epidemiologic interviewers. Amer. J. Epidemiol. 151: 199-205, 2000.

59. Hussain, S.P., Amstad, P., Raja, K., Ambs, S., Nagashima, M., Bennett, W.P., **Shields, P.G.**, Ham, A.J., Swenberg, J.A., Marrogi, A.J., Harris, C.C.: Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. Cancer Research 60:3333-3337, 2000.

60. Hussain SP, Raja K, Amstad PA, Sawyer M, Trudel LJ, Wogan GN, Hofseth LJ, **Shields, P.G.**, Billiar TR, Trautwein C, Hohler T, Galle PR, Phillips DH, Markin R, Marrogi AJ, Harris CC.: Increased p53 mutation load in nontumorous human liver of wilson disease and hemochromatosis: oxyradical overload diseases. Proc Natl Acad Sci U S A. 2000 Nov 7;97(23):12770-5.

61. Hussain SP, Amstad P, Raja K, Ambs S, Nagashima M, Bennett WP, Shields PG, Ham AJ, Swenberg JA, Marrogi AJ, Harris CC.: Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. Cancer Res. 2000 Jul 1;60(13):3333-7.

62. Goldman R, Day BW, Carver TA, Mauthe RJ, Turteltaub KW, **Shields PG.**: Quantitation of benzo(a)pyrene-DNA adducts by postlabeling with 14C-acetic anhydride and accelerator mass spectrometry. Chem Biol Interact. 2000 Jun 1;126(3):171-83.

63. Lerman C, Caporaso NE, Audrain J, Main D, Boyd NR, **Shields PG.:** Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependence. Mol Psychiatry. 2000 Mar;5(2):189-92.

64. Moysich KB, Freudenheim JL, Baker JA, Ambrosone CB, Bowman ED, Schisterman EF, Vena JE, **Shields PG.:** Apolipoprotein E genetic polymorphism, serum lipoproteins, and breast cancer risk. Mol Carcinog. 2000 Jan;27(1):2-9.

65. Butkiewicz D, Rusin M, Enewold L, **Shields PG**, Chorazy M, Harris CC.: Genetic polymorphisms in DNA repair genes and risk of lung cancer. Carcinogenesis. 2001 Apr;22(4):593-7.

66. Goldman R, Enewold L, Pellizzari E, Beach JB, Bowman ED, Krishnan SS, **Shields PG.** Smoking increases carcinogenic polycyclic aromatic hydrocarbons in human lung tissue. Cancer Res. 2001 Sep 1;61(17):6367-71.

67. Hussain SP, Amstad P, Raja K, Sawyer M, Hofseth L, **Shields PG,** Hewer A, Phillips DH, Ryberg D, Haugen A, Harris CC. Mutability of p53 hotspot codons to

benzo(a)pyrene diol epoxide (BPDE) and the frequency of p53 mutations in nontumorous human lung. Cancer Res. 2001 Sep 1;61(17):6350-5.

68. Lerman C, Caporaso NE, Bush A, Zheng YL, Audrain J, Main D, **Shields PG.** Tryptophan hydroxylase gene variant and smoking behavior. Am. J. Med. Genet. 2001 Aug 8;105(6):518-20.

69. Garte S, Gaspari L, Alexandrie AK, Ambrosone C, Autrup H, Autrup JL, Baranova H, Bathum L, Benhamou S, Boffetta P, Bouchardy C, Breskvar K, Brockmoller J, Cascorbi I, Clapper ML, Coutelle C, Daly A, Dell'Omo M, Dolzan V, Dresler CM, Fryer A, Haugen A, Hein DW, Hildesheim A, Hirvonen A, Hsieh LL, Ingelman-Sundberg M, Kalina I, Kang D, Kihara M, Kiyohara C, Kremers P, Lazarus P, Le Marchand L, Lechner MC, van Lieshout EM, London S, Manni JJ, Maugard CM, Morita S, Nazar-Stewart V, Noda K, Oda Y, Parl FF, Pastorelli R, Persson I, Peters WH, Rannug A, Rebbeck T, Risch A, Roelandt L, Romkes M, Ryberg D, Salagovic J, Schoket B, Seidegard J, **Shields PG,** Sim E, Sinnet D, Strange RC, Stucker I, Sugimura H, To-Figueras J, Vineis P, Yu MC, Taioli E.: Metabolic gene polymorphism frequencies in control populations. Cancer Epidemiol Biomarkers Prev. 2001 Dec;10(12):1239-48.

70. Caporaso NE, Lerman C, Audrain J, Boyd NR, Main D, Issaq HJ, Utermahlan B, Falk RT, **Shields P**. Nicotine metabolism and CYP2D6 phenotype in smokers. Cancer Epidemiol Biomarkers Prev. 2001 Mar;10(3):261-3.

71. Moysich KB, Ambrosone CB, Mendola P, Kostyniak PJ, Greizerstein HB, Vena JE, Menezes RJ, Swede H, **Shields PG,** Freudenheim JL.: Exposures associated with serum organochlorine levels among postmenopausal women from Western New York state. Am J Ind Med 2002 Feb;41(2):102-10.

72. Prochazka M, Granath F, Ekbom A, **Shields PG**, Hall P.: Lung cancer risks in women with previous breast cancer. Eur J Cancer. 2002 Jul;38(11):1520-5.

73. McCann SE, Moysich KB, Freudenheim JL, Ambrosone CB, **Shields PG**. The risk of breast cancer associated with dietary lignans differs by CYP17 genotype in women.J Nutr. 2002 Oct;132(10):3036-41

74. De Assis S, Ambrosone CB, Wustrack S, Krishnan S, Freudenheim JL, **Shields PG.** Microsomal Epoxide Hydrolase Variants Are Not Associated with Risk of Breast Cancer.Cancer Epidemiol Biomarkers Prev. 2002 Dec;11(12):1697-1698.

75. Epstein LH, Jaroni JL, Paluch RA, Leddy JJ, Vahue HE, Hawk L, Wileyto EP, **Shields PG**, Lerman C. Dopamine Transporter Genotype as a Risk Factor for Obesity in African-American Smokers. Obes Res. 2002 Dec;10(12):1232-1240.

76. Lerman C, **Shields PG,** Wileyto EP, Audrain J, Pinto A, Hawk L, Krishnan S, Niaura R, Epstein L. Pharmacogenetic investigation of smoking cessation treatment. Pharmacogenetics. 2002 Nov;12(8):627-634.

77. Benhamou S, Lee WJ, Alexandrie AK, Boffetta P, Bouchardy C, Butkiewicz D, Brockmoller J, Clapper ML, Daly A, Dolzan V, Ford J, Gaspari L, Haugen A, Hirvonen A, Husgafvel-Pursiainen K, Ingelman-Sundberg M, Kalina I, Kihara M, Kremers P, Le Marchand L, London SJ, Nazar-Stewart V, Onon-Kihara M, Rannug A, Romkes M,

Ryberg D, Seidegard J, **Shields P**, Strange RC, Stucker I, To-Figueras J, Brennan P, Taioli E. Meta- and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk. Carcinogenesis. 2002 Aug;23(8):1343-50.

78. Vineis P, Veglia F, Benhamou S, Butkiewicz D, Cascorbi I, Clapper ML, Dolzan V, Haugen A, Hirvonen A, Ingelman-Sundberg M, Kihara M, Kiyohara C, Kremers P, Le Marchand L, Ohshima S, Pastorelli R, Rannug A, Romkes M, Schoket B, **Shields P**, Strange RC, Stucker I, Sugimura H, Garte S, Gaspari L, Taioli E. CYP1A1 T3801 C polymorphism and lung cancer: A pooled analysis of 2,451 cases and 3,358 controls. Int J Cancer. 2003 May 1;104(5):650-7.

79. Patterson F, Benowitz N, **Shields P**, Kaufmann V, Jepson C, Wileyto P, Kucharski S, Lerman C. Individual differences in nicotine intake per cigarette. Cancer Epidemiol Biomarkers Prev. 2003 May;12(5):468-71.

80. Miksys S, Lerman C, **Shields PG**, Mash DC, Tyndale RF. Smoking, alcoholism and genetic polymorphisms alter CYP2B6 levels in human brain. Neuropharmacology. 2003 Jul;45(1):122-32.

81. Ambrosone CB, Moysich KB, Furberg H, Freudenheim JL, Bowman ED, Ahmed S, Graham S, Vena JE, **Shields PG.** CYP17 genetic polymorphism, breast cancer, and breast cancer risk factors. Breast Cancer Res. 2003;5(2):R45-51.

82. Freudenheim JL, Ram M, Nie J, Muti P, Trevisan M, **Shields PG**, Bandera EV, Campbell LA, McCann SE, Schunemann HJ, Carosella AM, Vito D, Russell M, Nochajski TH, Goldman R. Lung cancer in humans is not associated with lifetime total alcohol consumption or with genetic variation in alcohol dehydrogenase 3 (ADH3). J Nutr. 2003 Nov;133(11):3619-24.

83. Lerman C, **Shields PG,** Wileyto EP, Audrain J, Hawk LH Jr, Pinto A, Kucharski S, Krishnan S, Niaura R, Epstein LH.Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. Health Psychol. 2003 Sep;22(5):541-8.

84. Zheng YL, Loffredo CA, Yu Z, Jones RT, Krasna MJ, Alberg AJ, Yung R, Perlmutter D, Enewold L, Harris CC, **Shields PG**. Bleomycin-induced chromosome breaks as a risk marker for lung cancer: a case-control study with population and hospital controls. Carcinogenesis. 2003 Feb;24(2):269-74.

85. Audrain-McGovern J, Lerman C, Wileyto EP, Rodriguez D, **Shields PG**. Interacting effects of genetic predisposition and depression on adolescent smoking progression. Am J Psychiatry. 2004 Jul;161(7):1224-30.

86. Epstein LH, Wright SM, Paluch RA, Leddy JJ, Hawk LW Jr, Jaroni JL, Saad FG, Crystal-Mansour S, **Shields PG**, Lerman C. Relation between food reinforcement and dopamine genotypes and its effect on food intake in smokers. Am J Clin Nutr. 2004 Jul;80(1):82-8.

87. Xie H, Hou L, **Shields PG,** Winn DM, Gridley G, Bravo-Otero E, Diehl SR, Bowman ED, Brown LM, Hayes RB. Metabolic polymorphisms, smoking, and oral cancer in Puerto Rico. Oncol Res. 2004;14(6):315-20.

88. Lerman C, Berrettini W, Pinto A, Patterson F, Crystal-Mansour S, Wileyto EP, Restine SL, Leonard DG, Shields PG, Epstein LH. Changes in food reward following smoking cessation: a pharmacogenetic investigation. Psychopharmacology (Berl). 2004 Aug;174(4):571-7.

89. Ambrosone CB, McCann SE, Freudenheim JL, Marshall JR, Zhang Y, **Shields PG**. Breast cancer risk in premenopausal women is inversely associated with consumption of broccoli, a source of isothiocyanates, but is not modified by GST genotype. J Nutr. 2004 May;134(5):1134-8.

90. Smits KM, Benhamou S, Garte S, Weijenberg MP, Alamanos Y, Ambrosone C, Autrup H, Autrup JL, Baranova H, Bathum L, Boffetta P, Bouchardy C, Brockmoller J, Butkiewicz D, Cascorbi I, Clapper ML, Coutelle C, Daly AK, Muzi G, Dolzan V, Duzhak TG, Farker K, Golka K, Haugen A, Hein DW, Hildesheim A, Hirvonen A, Hsieh LL, Ingelman-Sundberg M, Kalina I, Kang D, Katoh T, Kihara M, Ono-Kihara M, Kim H, Kiyohara C, Kremers P, Lazarus P, Le Marchand L, Lechner MC, London S, Manni JJ, Maugard CM, Morgan GJ, Morita S, Nazar-Stewart V, Kristensen VN, Oda Y, Parl FF, Peters WH, Rannug A, Rebbeck T, Pinto LF, Risch A, Romkes M, Salagovic J, Schoket B, Seidegard J, **Shields PG,** Sim E, Sinnett D, Strange RC, Stucker I, Sugimura H, To-Figueras J, Vineis P, Yu MC, Zheng W, Pedotti P, Taioli E. Association of metabolic gene polymorphisms with tobacco consumption in healthy controls. Int J Cancer. 2004 Jun 10;110(2):266-70.

91. Lerman C, Wileyto EP, Patterson F, Rukstalis M, Audrain-McGovern J, Restine S, **Shields PG,** Kaufmann V, Redden D, Benowitz N, Berrettini WH. The functional mu opioid receptor (OPRM1) Asn40Asp variant predicts short-term response to nicotine replacement therapy in a clinical trial. Pharmacogenomics J. 2004;4(3):184-92.

92. Freudenheim JL, Bonner M, Krishnan S, Ambrosone CB, Graham S, McCann SE, Moysich KB, Bowman E, Nemoto T, **Shields PG**. Diet and alcohol consumption in relation to p53 mutations in breast tumors. Carcinogenesis. 2004 Jun;25(6):931-9.

93. Mechanic LE, Marrogi AJ, Welsh JA, Bowman ED, Khan MA, Enewold L, Zheng YL, Chanock S, Shields PG, Harris CC. Polymorphisms in XPD and TP53 and mutation in human lung cancer. Carcinogenesis. 2005 Mar;26(3):597-604. Epub 2004 Nov 25.

94. Joseph MA, Moysich KB, Freudenheim JL, **Shields PG,** Bowman ED, Zhang Y, Marshall JR, Ambrosone CB. Cruciferous vegetables, genetic polymorphisms in glutathione S-transferases M1 and T1, and prostate cancer risk. Nutr Cancer. 2004;50(2):206-13.

95. Colilla S, Lerman C, **Shields PG,** Jepson C, Rukstalis M, Berlin J, Demichele A, Bunin G, Strom BL, Rebbeck TR. Association of catechol-O-methyltransferase with smoking cessation in two independent studies of women. Pharmacogenet Genomics. 2005 Jun;15(6):393-398.

96. Marrogi AJ, Mechanic LE, Welsh JA, Bowman ED, Khan MA, Enewold L, **Shields PG**, Harris CC. TP53 mutation spectrum in lung cancer is not different in women and men. Cancer Epidemiol Biomarkers Prev. 2005 Apr;14(4):1031-3.

97. Redden DT, **Shields PG**, Epstein L, Wileyto EP, Zakharkin SO, Allison DB, Lerman C. Catechol-O-methyl-transferase functional polymorphism and nicotine dependence: an evaluation of nonreplicated results. Cancer Epidemiol Biomarkers Prev. 2005 Jun;14(6):1384-9.

98. El-Kafrawy SA, Abdel-Hamid M, El-Daly M, Nada O, Ismail A, Ezzat S, Abdel-Latif S, Abdel-Hamid A, **Shields PG**, Loffredo C. P53 mutations in hepatocellular carcinoma patients in Egypt. Int J Hyg Environ Health. 2005;208(4):263-70.

99. Xie B, Cummings SS, Singh B, He H, McCann S, Moysich K, Freudenheim JL, **Shields PG**. Accurate genotyping from paraffin embedded normal adjacent tissue of breast cancer. Carcinogenesis. 2005 Aug 19.

100. Prochazka M, Hall P, Gagliardi G, Granath F, Nilsson BN, **Shields PG,** Tennis M, Czene K. Ionizing radiation and tobacco use increases the risk of a subsequent lung carcinoma in women with breast cancer: case-only design. J Clin Oncol. 2005 Oct 20;23(30):7467-74.

101. Zheng YL, Loffredo CA, Alberg AJ, Yu Z, Jones RT, Perlmutter D, Enewold L, Krasna MJ, Yung R, **Shields PG**, Harris CC. Less efficient g2-m checkpoint is associated with an increased risk of lung cancer in African Americans. Cancer Res. 2005 Oct 15;65(20):9566-73.

102. Munafo MR, Johnstone EC, Wileyto EP, **Shields PG**, Elliot KM, Lerman C. Lack of association of 5-HTTLPR genotype with smoking cessation in a nicotine replacement therapy randomized trial. Cancer Epidemiol Biomarkers Prev. 2006 Feb;15(2):398-400.

103. Tennis M, Krishnan S, Bonner M, Ambrosone CB, Vena JE, Moysich K, Swede H, McCann S, Hall P, **Shields PG**, Freudenheim JL. p53 Mutation analysis in breast tumors by a DNA microarray method. Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):80-5.

104. Travis LB, Rabkin CS, Brown LM, Allan JM, Alter BP, Ambrosone CB, Begg CB, Caporaso N, Chanock S, DeMichele A, Figg WD, Gospodarowicz MK, Hall EJ, Hisada M, Inskip P, Kleinerman R, Little JB, Malkin D, Ng AK, Offit K, Pui CH, Robison LL, Rothman N, **Shields PG**, Strong L, Taniguchi T, Tucker MA, Greene MH. Cancer survivorship--genetic susceptibility and second primary cancers: research strategies and recommendations. J Natl Cancer Inst. 2006 Jan 4;98(1):15-25.

105. Natarajan TG, Ganesan N, Carter-Nolan P, Tucker CA, **Shields PG**, Adams-Campbell LL. {gamma}-Radiation-Induced Chromosomal Mutagen Sensitivity Is Associated with Breast Cancer Risk in African-American Women: Caffeine Modulates the Outcome of Mutagen Sensitivity Assay. Cancer Epidemiol Biomarkers Prev. 2006 Mar;15(3):437-42.

Review Papers, Editorials and Book Chapters (includes peer-reviewed review papers)

1. **Shields, P.G.** and Harris, C. C.: Environmental causes of cancer. Med. Clin. North Am. 74: 263-277, 1990.

2. Chase, K. C. and **Shields, P.G.**: Medical surveillance in PCB exposed persons. Occup. Med., State of the Art Rev. 5: 33-39, 1990.

3. Weston, A., Sugimura, H., Modali, R., Bowman, E. D., Caporaso, N. E., Manchester, D. K., **Shields, P.G.**, Poirier, M. C. and Harris, C. C.: Molecular dosimetry, genetic susceptibility and cancer risk. In Volans, G., Sims, J., Sullivan, F. and Turner, P. (Eds.): Basic Science in Toxicology: Proceedings of the V International Congress of Toxicology. Philadelphia, Taylor and Francis, Ltd., 1990.

4. **Shields, P.G.** and Harris, C. C.: Molecular epidemiology and the genetics of environmental cancer. JAMA 266: 681-687, 1991.

5. **Shields, P.G.**, Weston, A., Sugimura, H., Bowman, E. D., Caporaso, N. E., Manchester, D. K., Trivers, G. E., Tamai, S., Resau, J. H., Trump, B. F. and Harris, C. C.: Molecular epidemiology: dosimetry, susceptibility and cancer risk. In Vanderlaan, M., Stanker, L. H., Watkins, B. E. and Roberts, D. W. (Eds.): Immunoassays for Trace Chemical Analysis. Monitoring Toxic Chemicals in Humans, Foods and the Environment, Washington, D.C., American Chemical Society, 1991, pp. 186-206.

6. Sugimura, H., Weston, A., Caporaso, N. E., **Shields, P.G.**, Bowman, E. D., Metcalf, R. A. and Harris, C. C.: Biochemical and molecular epidemiology of cancer. In Chang, L. W. and Hart, R. (Eds.): Recent Advances in Biomarker Research. Academic Press, New York, 1991, pp. 73-92.

7. Lechner, J. F., Smoot, D. T., Pfeifer, A. M. A., Cole, K. H., Weston, A., Groopman, J. D., **Shields, P.G.**, Tokiwa, T. and Harris, C. C.: A non-tumorigenic human liver epithelial cell culture model for chemical and biological carcinogenesis investigations. In Rhim, J. S. and Dritschilo, A. (Eds.): Neoplastic Transformation in Human Cell Systems: Mechanisms of Carcinogenesis, The Humana Press, Inc., New Jersey, 1991, pp. 307-321.

8. **Shields, P.G.** and Chase, K. C.: Polychlorinated biphenyls and other polyhalogenated aromatic hydrocarbons. In Sullivan, J. B. (Ed.): Medical Toxicology of Hazardous Materials. New York, Williams and Wilkins, 1992.

9. Weston, A., **Shields, P.G.**, and Bowman, E. D.: Isolation of polycyclic aromatic hydrocarbon-DNA adducts from human lung. In: Garrigues, P. and Lamotte, M. (Eds.) Polycyclic Aromatic Hydrocarbons, Gordon and Breach Science Publ., France, 1992, pp. 937-944.

10. **Shields, P.G.**: Inherited factors and environmental exposures in cancer risk. J. Occup. Med. 35: 34-41, 1993.

11. **Shields, P.G.** and Harris, C. C.: Principles of Chemical Carcinogenesis. In DeVita, V. T., Hellman, S. and Rosenberg, S. A. (Eds): Cancer: Principles and Practice of Oncology, J.B. Lippincott Co., Philadelphia, PA. 4th Ed., 1993, pp. 200-213.

12. **Shields, P.G.**, Kato, S., Bowman, E. D., Petruzzelli, S., Cooper, D. P., Povey, A. C. and Weston, A.: Combined micropreparative techniques with synchronous fluorescence spectroscopy or ^{32}P-postlabeling assay for carcinogen-DNA adduct determination. In Phillips, D.H., Castegnaro, M. and Bartsch, H. (Eds.): Postlabeling Methods for Detection of DNA Adducts, IARC, Lyon, 1993, pp. 243-254.

13. Povey, A. C., Wilson, V. L., Weston, A., Doan, V. T., Wood, M. L., Essigmann, J. M. and **Shields, P.G.**: Detection of oxidative damage by ^{32}P-postlabeling: 8-hydroxydeoxyguanosine as a marker of exposure. IARC Sci. Publ., 124: 105-114, 1993.

14. **Shields, P.G.** and Harris, C. C.: Genetic predisposition to lung cancer. In Roth, J. A., Cox, J. D. and Hong, W. K. (Eds.): Diagnosis and Therapy of Lung Cancer, Blackwell Scientific Publications, Cambridge, 1993, pp. 3-19.

15. **Shields, P.G.** Clinical applications of molecular genetics. In McKunny, R. J. (eds.): Handbook of Occupational Medicine. Little, Brown & Co., 1994, pp. 418-427.

16. **Shields, P.G.**: Pharmacokinetics: Detecting sensitive populations. Environ. Health Perspect. Vol. 102, (Suppl. 11): 81-87, 1994.

17. Ambrosone, C. B., Kato, S., Bowman, E. D., Harrington, A. M., Blomeke, B., Freudenheim, J. L., Graham, S., Marshall, J. R., Vena, J. E., Brasure, J. R. and **Shields, P.G.**: Chemicals and Cancer. Euro. J. Cancer Prev., 5: 25-27, 1996.

18. **Shields, P.G.** and Yuspa, S.: Principles of Carcinogenesis: Chemical. In DeVita, V. T., Hellman, S. and Rosenberg, S. A. (Eds): Cancer: Principles and Practice of Oncology, J. B. Lippincott Co., Philadelphia, PA. 5th Edition, 1997, pp. 185-202.

19. Ambrosone, C. B. and **Shields, P.G.**: Molecular epidemiology of breast cancer. In Aldaz, C. M., Gould, M. N., McLachlan, J. and Slaga, T. J. (Eds.): Etiology of Breast and Gynecological Cancers. Wiley-Liss Inc., New York, 1997, pp. 83-99.

20. Warren, A. J. and **Shields, P.G.**: Molecular epidemiology: carcinogen-DNA adducts, and genetic susceptibility. Proc. Soc. Exper. Biol. Med. 216: 172-180, 1997.

21. Goldman, R. and **Shields, P.G.**: Molecular epidemiology of breast cancer. In Vivo, 12: 43-48, 1998.

22. **Shields, P.G.**: Genetic susceptibility to tobacco-related lung cancer. In: Mendelsohn, M. L., Mohr, L. C., Peeters, J. P. (Eds) Medical and Workplace Applications of Biomarkers. Joseph Henry Press, Natl. Acad. Of Sci., Washington, DC 1998, pp. 241-252.

23. Ambrosone, C. B. and **Shields, P.G.**: Smoking as a risk factor for cancer. In: Bowcouk, A (Ed), Breast Cancer. Humana Press, NJ. 1999.

24. Bennett, W. P., Hussain, S. P., Vahakangas, K. H., Khan, M. A., **Shields, P.G.**, and Harris, C. C.: Molecular epidemiology of human cancer risk: Gene-environment interactions and p53 mutation spectrum in human lung cancer. J. Pathol. 187: 8-18, 1999.

25. Lai, L., and **Shields, P.G.**: The role of interindividual variation in human carcinogenesis. J. Nutr. 129: 552S-555S, 1999.

26. Blomeke, B. and **Shields, P.G.**: Methods for Genetic Polymorphism Analysis. Metabolic Polymorphisms and Cancer. IARC Sci. Publ. 148: 133-148, 1999.

27. Freudenheim, J. L., Ambrose, B., Moysich, K. B., Vena, J. E., Graham, S., Marshal, J. R., Muti, P., Laughlin, R., Nemoto, T., Harty, L. C., Crits, G. A., Chan, A. W. K., and **Shields, P.G.**: Alcohol dehydrogenase 3 genotype modification of the association of alcohol consumption with breast cancer risk. Epidemiology. 10: 369-377, 1999.

28. Moysich, K. B., Freudenheim, J. L., Baker, J. A., Ambrosone, C. B., Bowman, E. D., Schisterman, E. F., Vena, J. E., and **Shields, P.G.**: Apolipoprotein E genetic polymorphism, serum lipoproteins, and breast cancer risk. Molecular Carcinogenisis. 5: 2-9, 2000.

29. **Shields, P.G.**: Molecular Epidemiology of Lung Cancer. Ann. Oncol. 10 Suppl. 5: S7-11, 1999.

30. **Shields, P.G.**: Publication bias is a scientific problem with adverse ethical outcomes: the case for a section for null results. Cancer Epidemiological Biomarkers Prev.. 9(8):771-772, 2000.

31. **Shields, PG.** and Harris,CC.:Cancer Risk and Low Penetrance Susceptibility Genes in Gene-Environment Interactions. Journal of Clinical Oncology. 18(11):2309-2315, 2000

32. **Shields, P.G.:** Epidemiology of Tobacco Carcinogens, Current Oncology Report. 2:257-262, 2000

33. Yuspa, S. and **Shields, P.G.:** Principles of Carcinogenesis: Chemical. In DeVita, V. T., Hellman, S. and Rosenberg, S. A. (Eds): Cancer: Principles and Practice of Oncology, J. B. Lippincott Co., Philadelphia, PA. 6th Edition, 2000.

34. **Shields, P.G.**, Whysner, J., and Chase, K. C.: Polychlorinated biphenyls and other polyhalogenated aromatic hydrocarbons. In Sullivan, J. B. (Ed.): Clinical Environmental Health and Exposures. Lippincott Williams and Wilkins. Philadelphia, PA. 2001.

35. Hemminki K, **Shields PG.**: Skilled use of DNA polymorphisms as a tool for polygenic cancers. Carcinogenesis. 2002 Mar;23(3):379-80.

36. **Shields PG**. Molecular epidemiology of smoking and lung cancer. Oncogene. 2002 Oct 7;21(45):6870-6.

37. **Shields PG**. Tobacco smoking, harm reduction, and biomarkers. J Natl Cancer Inst. 2002 Oct 2;94(19):1435-44.

38. Lee WJ, Brennan P, Boffetta P, London SJ, Benhamou S, Rannug A, To-Figueras J, Ingelman-Sundberg M, **Shields P**, Gaspari L, Taioli E. Microsomal epoxide hydrolase polymorphisms and lung cancer risk: a quantitative review. Biomarkers. 2002 May-Jun;7(3):230-41.

39. Goldman R, **Shields PG**. Food mutagens. J Nutr. 2003 Mar;133 Suppl 3:965S-973S.

40. Toraason M, Albertini R, Bayard S, Bigbee W, Blair A, Boffetta P, Bonassi S, Chanock S, Christiani D, Eastmond D, Hanash S, Henry C, Kadlubar F, Mirer F, Nebert D, Rapport S, Rest K, Rothman N, Ruder A, Savage R, Schulte P, Siemiatycki J, **Shields PG**, Smith M, Tolbert P, Vermeulen R, Vineis P, Wacholder S, Ward E, Waters M, Weston A. Links Applying new biotechnologies to the study of occupational cancer - a workshop summary. Environ Health Perspect. 2004 Mar;112(4):413-6.

41. Rebbeck TR, Martinez ME, Sellers TA, Shields PG, Wild CP, Potter JD. Genetic variation and cancer: improving the environment for publication of association studies. Cancer Epidemiol Biomarkers Prev. 2004 Dec;13(12):1985-6.

42. Yuspa, S. and **Shields, P.G.** Principles of Carcinogenesis: Chemical. In DeVita, V. T., Hellman, S. and Rosenberg, S. A. (Eds): Cancer: Principles and Practice of Oncology, J. B. Lippincott Co., Philadelphia, PA. 6th Edition, 2005.

43. Sugimura H and Shields PG. Methods for genetic testing I: Assessing mutations in cancers. In Cancer Risk Assessment. Shields, PG, (Editor). Taylor and Francis Group, LLC. Boca Raton, Florida. 2005.

44. Shields PG: Cancer risk assessment II: Methods for determining cancer etiology: assessing risks in individuals. In Cancer Risk Assessment. Shields, PG, (Editor). Taylor and Francis Group, LLC. Boca Raton, Florida. 2005

45. Shields PG. Cancer risk for tobacco and alcohol use. In Cancer Risk Assessment. Shields, PG, (Editor). Taylor and Francis Group, LLC. Boca Raton, Florida. 2005

46. Dumitrescu RG, Shields PG. The etiology of alcohol-induced breast cancer. Alcohol. 2005 Apr;35(3):213-25

47. Shields, PG and Chen J. Smoking and Carcinogenesis. In Molecular Mechanisms of Tobacco-induced Diseases. Xing Li Wang and David A Scott (Editors). Nova Science Publishers, Inc. New York, 2005

Book Editor

1. Carcinogens in the Workplace. Clinics in Occupational and Environmental Medicine. Volume 2, Number 4, 2002. W.B. Saunders, Phila., PA

2. Cancer Risk Assessment. Shields, PG editor. Taylor and Francis Group, LLC. Boca Raton, Florida. 2005.

Invited Presentations

1. N-Nitrosamine induced DNA damage detected by the ^{32}P-postlabeling assay. Laboratory of Human Carcinogenesis, NCI, Bethesda, MD, 1988.

2. Detection of polycyclic aromatic hydrocarbons-DNA adducts in human tissues. Laboratory of Human Carcinogenesis, NCI, Bethesda, MD, 1990.

3. CYP2D6 phenotyping, genotyping and lung cancer risk. Interlaboratory Seminar, Division of Cancer Etiology, NCI, Bethesda, MD, 1991.

4. Genetic predispositions to cancer. Conference on Integrating Cancer Prevention Practices in the 1990's. (Conference Chairman). George Washington University Medical Center, Washington, DC, 1991.

5. Genetic predisposition, formation of DNA adducts and human lung cancer risk. Aspen Cancer Conference, Aspen, CO, 1991.

6. Biological markers of risk for potential use in epidemiological studies of environmental ionizing radiation. Environmental Health Workshop, Sante Fe, NM, 1991.

7. Molecular epidemiology of lung cancer risk in Chinese women. Inhalation Toxicology Research Institute, Albuquerque, NM, 1991.

8. Pharmacokinetics: Detecting sensitive populations, pharmacokinetics in risk assessment. National Research Council, Irvine, CA 1992.

9. Molecular epidemiology of lung cancer. George Washington University Hospital, Washington, DC, 1992.

10. Environmental causes of cancer. George Washington University Hospital, Washington, DC, 1992.

11. Risk assessment of carcinogens in the workplace and environment--Inherited risk factors in cancer. American College of Occupational and Environmental Medicine. Washington, DC, 1992.

12. Molecular epidemiology and biomonitoring for chemical exposure. American College of Occupational and Environmental Medicine. Washington, DC, 1992.

13. Immunoaffinity chromatography and ^{32}postlabeling. International Meeting on Postlabeling Methods. Lyon, France, 1992.

14. Genetic predispositions to lung cancer. Department of Energy. Hyattsville, MD, 1992.

15. Inherited and acquired risk factors in lung cancer. Georgetown Univ. Hospital, Washington, DC, 1992.

16. Etiology of breast cancer--Tumor suppressor genes and oncogenes. American College of Radiology International Conference on Breast Cancer. Boston, MA, 1992.

17. Genetic predisposition and instability--Genetic alterations and cellular biology of bronchopulmonary tumors. Grenoble, France, 1993.

18. Polycyclic aromatic hydrocarbons and genetic susceptibility to lung cancer. Buffalo, NY, 1993.

19. Inherited and acquired predispositions to lung cancer. Lyon, France, 1993.

20. Inherited and acquired predispositions to lung cancer. George Washington University Hospital. Washington, DC, 1994.

21. Biomarkers for cancer susceptibility. American Society of Preventative Oncology. Washington, DC, 1994.

22. Evaluating cancer risk. George Washington University Hospital. Washington, DC, 1994.

23. Genetic polymorphisms and increased cancer risk. 8th International Conference on Carcinogen and Risk Assessment. Austin, TX, 1994.

24. Genetic and environmental risk factors for lung cancer. Interlaboratory Seminar. Division of Cancer Etiology, NCI. Bethesda, MD, 1994.

25. Cancer prevention in 1994 (Course Director). Denver, CO, 1994.

26. Evaluating cancer risk. Metropolitan Washington College of Occupational and Environmental Medicine. Bethesda, MD, 1994.

27. Genetic susceptibility of lung cancer. President's Lung Cancer Panel. Bethesda, MD, 1994.

28. Cigarette smoking and breast cancer. Interagency Working Group on Breast Cancer, Bethesda, MD, 1995.

29. Molecular epidemiology of lung and breast cancer. Society of Toxicology, Baltimore, MD, 1995.

30. Genetic susceptibility to cancer. Minisymposium. Chairman of Session, American Association of Cancer Research, Toronto, Canada, 1995.

31. Molecular epidemiology of lung and breast cancer. Genetic Target of Toxication-Induced Damage: Gordon Conference, MA, 1995.

32. Molecular epidemiology and cancer risk. Department of Pharmacology. George Washington University Medical Center, 1995.

33. Molecular epidemiology and cancer risk. School of Public Health. George Washington University Medical Center, 1995.

34. Cigarette smoking and N-acetyltransferase genetic polymorphisms. National Cancer Institute Advisory Board. National Cancer Institute, Bethesda, MD, 1995.

35. Genotyping polymorphisms and smoking in defining breast cancer risks. 9th International Conference on Carcinogenesis and Risk Assessment, Austin, TX, 1995.

36. Molecular epidemiology of breast cancer. Conference on Chemoprevention, Easton, MD, 1995.

37. Gene-environment interactions. University of Maryland Cancer Center, Baltimore, MD, 1995.

38. Molecular epidemiology. National Capital Occupational Medicine Association, Washington, DC, 1996.

39. NAT2 and breast cancer. Intralaboratory seminar. National Cancer Institute, Bethesda, MD, 1996.

40. Cancer susceptibility genes. Conference on cancer susceptibility. Keystone, CO, 1996.

41. Carcinogenesis. George Washington University School of Public Health, Washington, DC, 1996.

42. Molecular epidemiology. Congress on Causes of Cancer, Udine, Italy, 1996.

43. Molecular epidemiology of lung and breast cancer. Shanghai Cancer Institute, Shanghai, China, 1996.

44. Biomarkers of xenobiotic exposure. Canadian Society of Toxicology, Montreal, Canada, 1996.

45. Molecular epidemiology for risk assessment. Society for International Risk Assessment, New Orleans, LA, 1996.

46. Molecular epidemiology of lung and breast cancer. Georgetown University, Washington, DC, 1997.

47. Genetic susceptibility to cancer. Society of Toxicology, Cincinnati, OH, 1997.

48. Molecular epidemiology of tobacco smoking. Assessment of Cancer in the Human, Venice, Italy, 1997.

49. P450 and chemical metabolism. Biomarkers, the Genome and the Individual, Charleston, SC, 1997.

50. Tobacco, alcohol and cancer risk. MD Anderson Cancer Center. Houston, TX, 1997.

51. Molecular epidemiology of lung and breast cancer. Johns Hopkins University, Baltimore, MD 1997.

52. Molecular epidemiology. Howard University Medical Center, Washington, DC, 1997.

53. Gender differences in cancer. Healthy Women 2000 Conference, Washington, DC, 1997.

54. Round-table discussion for prostate cancer. Reston, VA, 1997.

55. Round-table discussion for breast cancer. Baltimore, MD, 1997.

56. Gene-environment lifestyle interactions for breast cancer. Molecular Carcinogenesis and molecular epidemiology of cancer. Maui, Hawaii, 1998.

57. Molecular epidemiology overview. Environmental Mutagen Society, Anaheim, CA, 1998.

58. Molecular epidemiology overview. American Society of Preventive Oncology, Washington, DC, 1998.

59. Carcinogenesis and interindividual variation. American Society of Nutritional Sciences, San Francisco, CA, 1998.

60. Molecular genetics. 3rd International Congress on Cancer. Venice, Italy, 1998.

61. Case control and cohort studies. Clinical Implications of Molecular Epidemiology of Human Lung Cancer. Norwegian Cancer Society. Oslo, Norway, 1998.

62. Molecular epidemiology of lung and breast cancer. Lawrence Livermore National Laboratory. Livermore, CA, 1998.

63. Gene-Environment Inventory for Cancer Risk and Behaviors. British Association of Cancer Research. London, England, 1998.

64. Molecular Epidemiology of Cancer Risk. Gene Environment Interaction in Human Health. Cincinnati, OH, 1998.

65. Molecular Epidemiology of Cancer. 2nd Mid Atlantic Regional Conference On Occupational Medicine. Williamsburg, VA, 1998.

66. Etiology of Head and Neck Cancer. Session Leader and Lecturer. Head and Neck Cancer Workshop, Bethesda, MD, 1999.

67. Chairperson in Session on Molecular Epidemiology. AACR Annual meeting. Philadelphia, PA, 1999.

68. Genetic Basis of Cigarette Smoking. American Society of Preventive Oncology, Houston, TX, 1999.

69. Molecular Epidemiology. Dartmouth Medical School. Hanover, NH, 1999.

70. Low penetrance genes. Georgetown University, Washington, DC, 1999.

71. Molecular Epidemiology of Cancer Risk. Mayo Clinic, Rochester, MN, 2000.

72. Mutagenesis and Mutagenic Spectra. Mechanisms of Carcinogenesis. Washington, DC, 2000.

73. Tobacco smoking and Breast Cancer. American Chemical Society. Washington, DC, 2000.

74. Tobacco Associated Cancers. Chronic Radiation Exposure: Possibilities of Biological Indication. Chelyabinsk, Russia, 2000.

75. Novel Methods for Risk Assessment. American Association of Cancer Research Annual Meeting. Poster Discussion Leader. San Francisco, CA, 2000.

76. Genetics of Tobacco Addiction. American Association of Cancer research Annual Meeting. San Francisco, CA, 2000.

77. Cancer Genetics and Cancer Risk. Mechanisms of Toxicity. Gordon Conference. 2000.

78. Program Organizer . Joint U.S. - Japan Research Conference on Tobacco and Lung Cancer. Hawaii, 2001.

79. Low Penetrance Susceptibility Genes In Gene-environment Interactions Life Sciences Institute Annual Meeting. Jamaica, 2001.

80. Symposium Speaker. American Society of Preventive Oncology. New York, NY 2001

81. Cancer Genetics and Risk. Washington Hospital Center. Washington, DC 2001

82. Genetics of Tobacco Addiction. AACR Educational Session. New Orleans, LA. 2001

83. Poster Discussion Leader. AACR Annual Meeting, New Orleans, LA. 2001

84. Genetic Susceptibility to Tobacco-Related Cancer. Reducing Tobacco Harm Conference. Minneapolis, MN 2001.

85. Genetic Determinants of Cancer Risk. Functional Genomics" in Human Populations: Understanding Cancer in the Post-Genome Era. University of Pennsylvania, Phil. PA. 2001.

86. Molecular Epidemiology of Lung and Breast Cancer. Mount Sinai School of Medicine. New York, NY 2001

87. Tobacco Smoking and Harm Reduction. American Society of Preventive Oncology. Washington, DC 2002

88. Session Moderator: Point Counter Point – A Priori Hypotheses and New Technologies. American Association of Cancer Research, San Francisco, CA 2002

89. Chairperson: DNA Repair and Cancer Risk. American Association of Cancer Research, San Francisco, CA 2002

90. Chairperson: Gene Pathways to Cancer. American Association of Cancer Research, San Francisco, CA 2002

91. Molecular Epidemiology. University of Manchester, England, 2002

92. Oxidative Damage and Cancer Risk. P20 Workshop for Nutrition Center at University of Connecticut. New York, New York. 2002

93. Harm Reduction. American Association of Cancer Research Frontiers in Prevention Research. Boston, MA. 2002

94. Methylation in Lung and Breast Cancer Risk. Karolinska Institute, Stockholm, Sweden, 2002.

95. Molecular Epidemiology. National Cancer Institute Program for Cancer Prevention Fellows. Bethesda, MD 2002.

96. Pathobiology of Cancer and the Rationale of Assessing Intermediate Biomarkers. Applying New Biotechnology to theStudy of Occupational Cancer. Washington, DC 2002

97. Molecular Epidemiology of Breast Cancer. Roswell Park Cancer Institute. Buffalo, NY 2002

98. Genotype and Phenotype Relationships for Breast Cancer Risk. Molecular and Genetic Epidemiology. Hawaii, 2003

99. Breast and Lung Cancer. Johns Hopkins University, Baltimore, MD. 2003

100. Tobacco Smoking and Lung Cancer. Georgetown University Department of Medicine Ground Rounds. Washington, DC 2003.

101. Cigarette Use, Addiction and Harm. University of the District of Columbia. Washington, DC 2003

102. Peer-Review Publishing. American Society of Preventive Oncology Annual Meeting. Philadelphia, PA 2003

103. Discussant. Linking Haplotpes and Genetic Variation With Cancer Risk Assessment, Prevention, Detection and Treatment Workshop. Bethesda, MD 2003

104. Tobacco Smoking and Products That Kill When Used As Intended. Georgetown University Department of Medicine Grand Rounds, Washington, DC 2003

105. Tobacco Smoking and Products That Kill When Used As Intended. Continuing Education Program. Georgetown University School of Nursing and Health Sciences, Washington, DC 2003

106. The Genetic Basis of Tobacco Addiction. Pharmacogenomics Workshop. Rockville, MD 2003

107. Discussant. Methods and Biomarkers to Assess Reductions in Tobacco Toxin Exposure. Washington DC 2004

108. Interindividual Variation in Cell Culture Phenotypes. Symposia Presentation. Role of DNA Repair Genotype and Phenotype in Cancer Susceptibility. AACR Annual Meeting, Orlando, FL 2004

109. Molecular Epidemiology of Tobacco Use and Harm. University of Minnesota Transdisciplinary Tobacco Use Research Center. Minnealolis, Minnesota 2004

110. Molecular Epidemiology of Cancer Risk. Memorial Sloan-Kettering. New York, New York 2004

111. Biomarkers and Breast Cancer Risk. Alcohol and Alcoholism Workshop, NIAAA. Bethesday Maryland 2004

112. Genetics of Smoking Addiction. Georgetown University School of Nursing and Health Sciences. Washington, DC 2004

113. Tobacco Use and Harm. AACR Special Conference on Lung Cancer. San Diego, CA 2005

114. Molecular Epidemiology of Breast Cancer. Howard University. Washington, DC 2005

115. Biomarkers of carcinogen uptake and activation. Amercian Chemical Society. Washington, DC 2005

116. Harm Reduction and New Tobacco Company Products. Multidisciplinary Lung Conference. Georgetown University Medical Center. Washington, DC 2005

117. Molecular Epidemiology of Lung Cancer. Laboratory of Human Carcinogenesis. National Cancer Institute. Bethesda, MD. 2005

118. Harm Reduction and New Tobacco Company Products. Department of Medicine Grand Rounds. Georgetown University Medical Center. Washington, DC 2005

119. Genetics of Smoking Addiction and Harm. U.S. Japan Cooperative Cancer Research Program. Molecular Epidemiological Characteristics of Lung and Colon Cancer Development Among Atomic Bomb Survivors. Bethesda, MD. 2006.

120. Molecular Epidemiology of Breast Cancer. International Symposia of Human Carcinogenesis. National Institutes of Health. Bethesda MD. 2006

121. Choosing Haplotypes, SNPs or Phenotypes to Study. Methods Workshop: Haplotyping Methodology, What’s Nuts and Bolts. American Association For Cancer Research. Washington, DC 2006.

EXHIBIT 2

Peter G. Shields, MD
1145 Millcreek Lane
Columbus, Ohio 43220

February 28, 2014

Heather Forgey, Esq.
Jones, Carr, & McGoldrick
Premier Place
5910 N. Central Expressway, Suite 1700
Dallas, TX 75206

re: Campos v Safety-Kleen

Dear Ms. Forgey:

This report will summarize my opinions for the above cited case as it relates to Mr. Gerardo Campos' development of chronic myelogenous leukemia (CML) and his workplace with use of a Safety-Kleen parts washer with Safety-Kleen 105 solvent. He worked as a precision tool repairman. I have reviewed several types of documents for this case, which are listed below, including legal documents, medical records, material safety data sheets, internal Safety-Kleen documents, monitoring reports and expert reports. At the end of this report is a list of references cited herein, which are not necessarily all inclusive, but are extensive and representative of the studies and publications that support my opinions. The opinions expressed herein are my own, and were not developed in relationship to my Ohio State University service. If additional materials are provided to me after the submission of this report, then my opinions may be supplemented or changed.

TABLE OF CONTENTS

QUALIFICATIONS

As my *Curriculum Vitae* will provide in more detail, I am currently a tenured Professor in the Departments of Internal Medicine in the College of Medicine and the Department of Epidemiology at the College of Public Health at The Ohio State University. I also am an adjunct Professor at Georgetown University, adjunct Professor in the Department of Pediatrics and Child Health at the Howard University School of Medicine, and an adjunct Professor in the Department of Biological Sciences and Environmental Health at the University of the District of Columbia. At The Ohio State University, I am the Deputy Director of the OSU Comprehensive Cancer Center, having assumed this position as of September 1, 2011. Prior to that, for 11 years I worked at Georgetown University, where I was the Deputy Director of the Lombardi Comprehensive Cancer Center. Other positions that I have held in the past several years at Georgetown include Interim-Chair of the Department of Medicine, Chief of the Division of Cancer Genetics and Epidemiology in the Department of Oncology, Vice-Chair of the Department of Oncology and Associate Director for Cancer Control and Population Sciences. As such, I have been responsible for directing a multidisciplinary and transdisciplinary research program that focuses on identifying the environmental and genetic causes of cancer using epidemiology and biomarkers. Through all these activities, I am responsible for mentoring many junior and senior faculty, postdoctoral fellows, PhD, medical students, interns, residents, master's graduate students, and undergraduate students. My teaching responsibilities include, or have included, leading the academic mission of the Department of Medicine at Georgetown University, giving lectures and serving as a course director in the areas of cancer risk and epidemiology. Prior to my position at the Lombardi Comprehensive Cancer Center, I was a tenured investigator and Chief of the Molecular Epidemiology Section of the Laboratory of Human Carcinogenesis at the National Cancer Institute.

My *Curriculum Vitae* shows that I have published more than 200 papers in scientific journals, many in high-impact journals, and I serve, or have served, on the editorial boards of important journals such as *Carcinogenesis; Molecular Carcinogenesis; Journal of Cancer Epidemiology;* and, *Cancer, Epidemiology, Biomarkers and Prevention.* As evidence of the respect from my peers, I have been elected as President of the American Society of Preventive Oncology and have just completed that service, and was the first elected chair to lead the Molecular Epidemiology Group of the American Association of Cancer Research. Recently, I was elected as a Fellow of the American College of Epidemiology. Over the years, I have been the Program Chair or member of numerous program committees for national and international scientific meetings. Regularly, I am an invited speaker at national and international meetings, and at universities around the world. I also sit on various committees and panels that provide research opinions, identify funding priorities or review other investigators' research proposals about the causes of cancer. For example, I have served on the National Institutes of Health Study Section that reviews Comprehensive Centers (Subcommittee B), the NCI Clinical Trials Advisory Committee, and was a standing member of the Epidemiology and Disease Control 2 NIH study section. In the past, I have served on the National Cancer Institute's (NCI) Tobacco Research Implementation Group, NCI Lung Cancer Progress Review Group, and also on the Institute of Medicine Committee on Tobacco Harm Reduction.

Throughout my career, I have conducted research into the chemical and genetic causes of

cancer, as well as the development of tests for cancer risk and early detection of cancer. And in doing so, I regularly conduct epidemiological studies. Relevant to the case addressed here, I am an expert in the development of cancer and have published widely in this area, and have served on numerous committees that have considered this particular area of science. My publications, which include those that relate directly to some of the chemicals at issue here, have appeared in highly respected peer-reviewed journals (including those that focus on the occupational and environmental setting). Also relevant to this evaluation is that my work is considered toxicological in nature, because of the consideration of how carcinogens or cancer therapies affect the body, I frequently use laboratory methods (including animal studies), and I have published toxicology studies.

Lastly, I remain clinically active by caring for oncology patients. My clinical expertise has been recognized as I have been twice appointed to the District of Columbia Board of Medicine, which is a board that sets medical practice guidelines, grants licenses and disciplines physicians. And I have been provided awards for my work with charity patients, and have been cited as a Castle Connolly's Top Doctor for Cancer in multiple years, as recently as 2014. Thus, I consider myself an expert in cancer risk, cancer causation, carcinogenesis, epidemiology, and hematology/oncology.

DOCUMENTS REVIEWED

Legal Documents

- Declaration of Gerardo Campos (11/16/13)
- Defendant Safety-Kleen Systems, Inc.'s Objections and Responses to Plaintiffs' First Request To Produce (12/23/13)
- Defendant Safety-Kleen Systems, Inc.'s Objections and Answers to Plaintiffs' First Set of Interrogatories (12/23/13)
- Plaintiffs' Disclosure of Expert Witnesses
- Complaint (6/29/12)
- Amended Complaint (11/2/12)
- Answers to Amended Complaint - Makita (1/15/13)
- Defendant Safety-Kleen Systems, Inc.'s Answer and Defenses to Plaintiffs' Complaint (10/2/12)
- Defendant Safety-Kleen Systems, Inc.'s First Amended Answer and Defenses to Plaintiffs' Amended Complaint (12/20/12)
- Notice of Serving Plaintiff Camilla Campos' Answers to Defendant Makita's Interrogatories (7/24/13)
- Notice of Serving Plaintiff Gerardo Campos' Response to Defendant Makita's Request for Production (12/9/13)
- Notice of Serving Plaintiff Gerardo Campos' Response to Defendant Makita's Request Interrogatories (7/24/13)
- Rule 26 Initial Disclosure (11/19/13)
- Notice of Serving Plaintiff Yadira D. Veguilla Rosario's Response to Defendant Makita's Request Interrogatories (8/30/13)
- Deposition of Gerardo Campos (12/18/13)
- Deposition of Carmen B Campos Diaz (12/19/13)

- Deposition of Nydia Rosario-Colon (12/19/13)
- Deposition of Yadira VeguillaRosario (12/19/13)

Medical and other Documents

- Jose Comancho, MD
- Jose Carlo, MD
- Luis Ramos, MD
- Maria Garcia, MD
- Hato Rey, MD
- University of Puerto Rico
- Various documents produced by Makita
- Safety-Kleen Production Bates SKS_CAMP000001-000312

Expert Reports

- Su-Jung Tsai (12/10/13)
- Arthur Frank (12/13/13)
- David Goldsmith (12/13/13)
- Melvin Kopstein (12/13/13)

ALLEGATIONS

The complaint states that Mr. Campo worked from 1993 to 2010 with Safety-Kleen 105. (His declaration stated 1995 to 2010, and Makita records indicate a start date of December 4, 1995.) The complaint stated "Safety-Kleen 105 Solvent is contaminated with multiple carcinogenic chemicals, including benzene, perchloroethylene, trichloroethylene, methylene chloride, chlorinated benzenes, and polycyclic aromatic hydrocarbons." It then stated that as a result of the exposure, Mr. Campos developed chronic myelogenous leukemia. Expert reports for the plaintiff have focused mostly on a putative benzene exposure.

SCOPE OF OPINIONS AND BASIS FOR THEM

I have been asked to evaluate the medical history of Mr. Campos and provide an opinion regarding his diagnosis of CML. Also, I have been asked to provide opinions generally regarding risks for CML, and epidemiology related to work that would include exposure to mineral spirits and benzene. I have been asked if the alleged exposures could be considered to have caused or contributed to Mr. Campos' CML. I also have been asked to provide a description for the methods to assess general and individual causation of cancer, and to evaluate the methodologies, factual basis for the opinions and the conclusions of plaintiff's expert's reports. I have reviewed Mr. Campos' medical records, which forms the basis for my understanding of what his medical condition was, and his alleged and real risk factors for CML. My opinions are formulated based upon my general scientific and medical knowledge, my comprehensive literature review, my research and my clinical practice as a hematologist and oncologist. I rely upon a number of sources including general knowledge, textbooks, reports of

regulatory and review agencies, and peer-reviewed scientific studies. I have performed computerized literature searches through the National Library of Medicine (PubMed) that included search terms such as leukemia, cancer, benzene, mineral spirits, gasoline, printers, mechanics, gas station, and others. These types of activities are not very different from my regular day-to-day activities as a clinician, researcher and educator. For example, my research involves the study of cancer risk and I regularly have to interpret data and communicate such in scientific journals and to the lay public. Another example is that I frequently give lectures to the public and physicians about the causes of cancer, how to screen for it and how to prevent it.

Related to the above and my expertise, I can offer opinions about toxicology, carcinogenesis (including the development of CML), epidemiology, cancer risk and general causation. As a trained clinician, I also will offer opinions about Mr. Campos' CML and his risk factors for these, and well as a specific causation opinion.

MEDICAL RECORD REVIEW

Mr. Gerardo Campos was born on May 28, 1967. He was diagnosed with CML in November, 2011 at the age of 44. Mr. Campos has a history of Charcot Marie Tooth.

The Charcot Marie Tooth disorder originally became symptomatic around the age of 14 with weakness of the lower extremities. In 1997, he had a bilateral foot drop, and was given devices to assist him. Three cousins on his mother's side also had the disease. In 2002, it was reported that his neurological problems were worse with increased difficulty playing guitar, although his lower extremity weakness was stable. In 2005 it was stated that he was currently disabled due to his neurological disorder. Mr. Campos had nerve conduction testing on February 2, 2012, which was consistent with a demyelinating hereditary neuropathy. It was reported that he had a history of dengue fever.

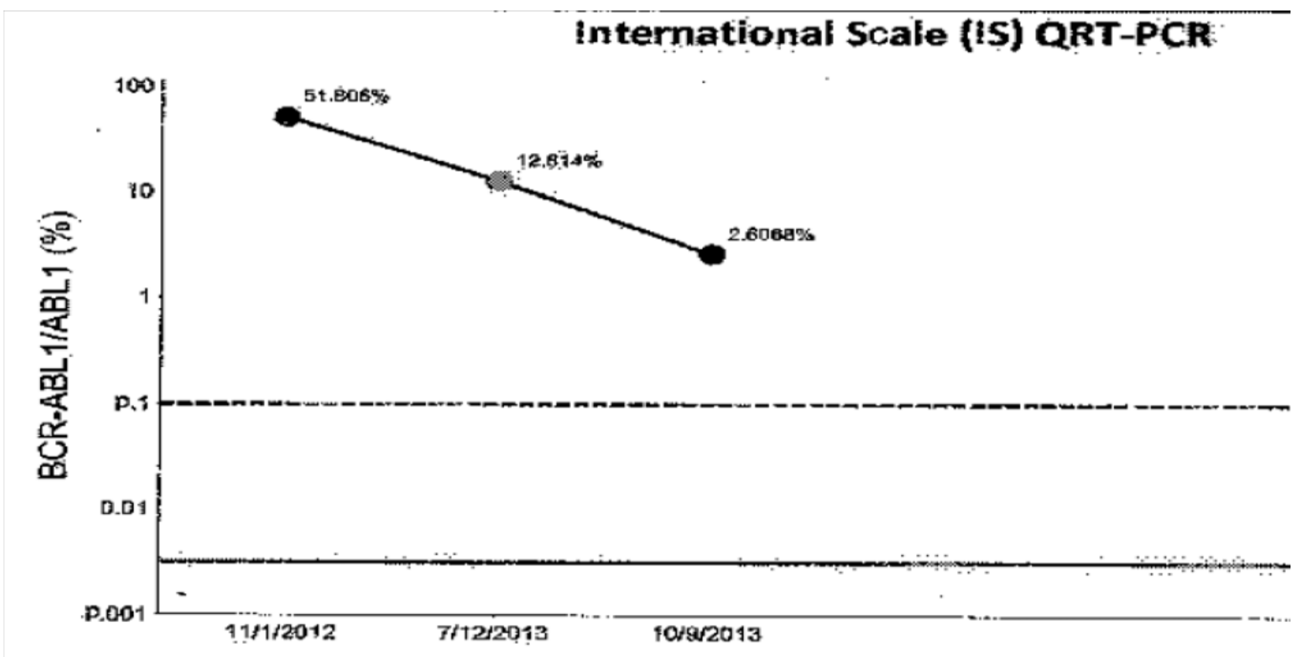
Medical records indicate that Mr. Campos was treated with Wellbutrin in 2002 and 2004. He was diagnosed with recurrent depression in 2008. In 2012, Mr. Campos was seen by a psychiatrist who diagnosed an adjustment disorder.

Mr. Campos presented for a pre-op evaluation to have papilloma removed from the groin area. He was found incidentally with a high WBC. The WBC was 76.8, platelets were 562 and the HCT was 40.8. The AST was 23 and the ALT was 71. There were promyelocytes, myelocytes and metamyelocytes observed, but no blasts. He had palpable splenomegaly. On November 8, 2011, a bone marrow was done. It was reported to have very active platelet production, be markedly hypercellular, have increased markedly megakaryocytes, dysmegakaryopoeisis, increased micromegakaryocytes, decreased erythroid series relative to the granulocytes, and a shift to the left for granulocytes with occasional blasts. It was stated that the marrow was reactive compatible with a myeloproliferative disorder. The karyotype was 46, XY t(9:22)(q34;q11.2), which was confirmed by FISH. BCR/ABL PCR was 100%. The peripheral smear had normal morphology but a shift to the left with marked leukocytosis. On November 15, 2011 it was stated he was on hydrea but was being changed to Gleevec. His WBC was 56k, platelets 543k and the HCT was 38%.

On March 12, 2012, Mr. Campos was on Gleevec. His WBC was 6.89, HCT was 44.6% and the platelets were 192k. Although around that time he had Gleevec held due to cytopenias.

On August 15, 2012, it was stated he had pancytopenia secondary to Gleevec, so he was changed to disatinib. His BCR/ABL increased from 21% to 70%. He was originally started on disatinib 100/day, but had to be decreased to 50 every other day. He remained asymptomatic according to the records. On December 12, 2012, his WBC was 3.8 and the platelets were 86k. He was again reported to be asymptomatic. The On January 16, 2013, a bone marrow was done. The report said that blasts were not identified, and that the marrow was consistent with a complete remission. The peripheral smear was reported with normal morphology. Results were similar to before, except the BCR/ABL was up to 100%.

It was stated on June 10, 2013, Mr. Campos was feeling well. On July 10, 2013, the BCR/ABL was 12%. On October 9, 2013, the WBC was 2.9, Hgb was 13.1 and the platelets were 82k. BCR/ABL was 2%. Below is a graph of his trend.



At deposition, Mr. Campos said his CML caused him to have stomach pain from inflammation of the spleen, back pain, and extreme fatigue. The symptoms reportedly started about 6 months before his diagnosis. He also said he gets a flu every month due to the chemotherapy. He reported he never had radiation and no family history of blood disorders.

Mr. Campos' wife, in interrogatories, stated: "As a result of my husband diagnosis has

been absent due to his sickness. Most of his time he is at doctors' appointments or at rest because of the disease. This means that because of his disease he misses time with me and missed special events of our family and our daughter Camila, who has only 1 year old when he wad diagnosed with the disease. Also, I miss time from work consequently, not only to be with my husband at his medical appointments but also, because of my mental health. Also my relationship with my husband has changed since his diagnostic, we are constantly worrying and we lack of sexual activity." In 2004, a discrimination complaint authored by Mr. Campos stated the he was suffering from insomnia, sexual dysfunction and eating disorders. Mr. Campos' wife corroborated her statement at deposition.

Family History: No blood diseases. Mother with breast cancer. Two aunts with breast cancer. Cousin with breast cancer. Cousin with liver cancer. Father with skin cancer.

<u>Smoking</u>
2008 - Marijuana use
2011 - quit 1 year earlier; 15 pack years

At deposition, Mr. Campos testified that he smoked beginning at age 18 and quit in 2011, with some gaps in smoking. He also testified he smoked marijuana since the age of 17, sometimes daily.

<u>Alcohol</u>
2011 - occasional beer

<u>BMI</u>
5'8"
1997 - 144 pounds
2005 - 148 pounds
2012 - 152 pounds
2013 - 160 pounds

Occupational History: Mr. Campos' declaration stated that he worked with Safety-Kleen Solvent 105 from 1995 - 2010 while employed at Makita USA (1995-2004), National Rental Sales (2006-2010) and Tool Box (2010-2011). Makita records indicated a start date of December 4, 1995, and that he was a factory service manager and then became a power tool technician. He stated that the solvent would splash on his clothes and face. He wore rubber gloves. He reported that about 2 times a month he would repair gasoline-powered equipment. At deposition, Mr. Campos stated he used the parts washer about 10 times per day, between 12-20 minutes each time. He stated that sometimes he would wear gloves provided by Safety-Kleen depending on how long he would need to wash the part. Also, he said that sometimes he would clean his hands with the solvent. At the other workplaces, he used the parts washer similarly or less.

Prior to the above, the reported work history is 1992-1994 Astro Industrial Supply that made cables for towing ships -warehouse employee and power tools technician and 1995 Ferreteria Abraham that was an industrial hardware store - power tools technician. At deposition, Mr. Campos also said he worked at a clothing store and an electrical equipment store. He denied chemical exposures for all of these jobs.

DISCUSSION

Mr. Campos has CML, which is a type of chronic leukemia. He presented incidentally with typical findings, namely an elevated white blood cell count, and without symptoms. The molecular and cytogenetic work-up confirmed the diagnosis of CML. Mr. Campos has a 9,22 translocation, which is diagnostic for CML. Mr. Campos received the diagnosis of the CML from his treating physicians, and I concur with this diagnosis, although I have not reviewed the actual pathology slides.

Leukemias are one type of many hematological malignancies. All of these are clonal disorders that are composed of a single and specific cell type. As with other types of cancers, the cells of these clonal stem cell disorders fail to differentiate and reproduce uncontrollably, crowding out space for normal bone marrow elements. Actually, leukemias also are a heterogeneous group of blood cell malignancies. They are classified as acute or chronic, and originate from either myeloid or lymphoid lineages The diagnosis of leukemia is made by examining the bone marrow with a microscope, flow cytometry, immunohistochemisty and chromosomal analysis. Among the reasons why it is important to identify the type of leukemia is that the etiology, biology, treatment and prognosis can be very different.

CML is an uncommon disorder, accounting for about 5,920 new cases in the US in 2013 [1]. This is among a total of 48,610 new cases of all leukemia and about a third as common as AML with about 14,590 cases per year. The annual incidence of CML is 1.6 cases per 100,000 adults.

CML is classified as a myeloproliferative disorder, but is very different from other myeloproliferative disorders because of its Philadelphia chromosome positivity [2-5]. All of these also have very different clinical histories and treatments, although there may be some overlap as one develops overtime. The hallmark of CML is the finding of the Philadelphia chromosome, which is a translocation of the *BCR-ABL* genes on chromosomes 9 and 22. Although CML is manifested primarily as an abnormality in the white cell lines, the chromosome abnormality is seen in all cell lines. The laboratory findings are a leukocytosis in the blood, with an increased number of neutrophil precursors, but not blasts. There is no significant dysplasia, distinguishing it from myelodysplastic syndromes. Also seen in the blood is an increase of basophils, and sometimes eosinophils. The platelet count may be elevated, but not depressed, also distinguishing it from MDS and AML. In the bone marrow, the hyperplasia of the white blood cell line is seen, without an increase in blasts unless the patient is in the later

stages of CML. There can be megakaryocytic proliferation and the megakaryocytes are small and hypolobulated.

CML clinically has three phases, namely the chronic phase, the accelerated phase and the blast phase [6]. Mr. Campos is currently in the chronic phase. Patients frequently present in the chronic phase (about 40%), without symptoms, and the disease is detected by a routine blood test [7]. Eventually, patients may complain of weakness, weight loss and discomfort due to a large spleen. The accelerated and blast phases are now uncommon due to recent therapies. The criteria for blast phase include a blast count in the bone marrow greater than 20%, depending on the criteria [6]. Evolution is usually accompanied by additional genetic abnormalities, such as an extra Philadelphia chromosome, +8, +19 or i(17q).

The Philadelphia chromosome is a reciprocal translocation from chromosome 9 to chromosome 22 that involves the *ABL1* gene on chromosome 9 and the *BCR* (break point cluster) gene on chromosome 22 [5;7]. This is termed the *BCR-ABL* translocation. The resultant gene fusion makes a protein that has tyrosine kinase activity. This protein leads to deregulated cellular proliferation, cells that are less able to adhere to the bone marrow and decreased program cell death in response to mutagens. Targeting the tyrosine kinase activity, the so-called tyrosine kinase inhibitors (TKI) is what has made the remarkable treatments available for this disease. In the past, there was an entity of Philadelphia chromosome-negative CML, but these were based on cytogenetics and molecular phenotyping now either show a cryptic translocation or the disease is not CML. The site of where the breakpoint is may influence the clinical course of CML. The breakpoint regions can also distinguish CML from CMML and ALL, which also can have the Philadelphia chromosome.

The postulated cell of origin is unclear, and while it is likely that the abnormalities start in a hematopoietic stem cell, the phenotype of the disease is thought to happen in more committed precursors of the granulocytic-macrophage progenitor pool [6].

Sometimes, other cytogenetic abnormalities are seen in CML, such as trisomy 8, isochromosome 17 and a duplicate Philadelphia chromosome [6], but these are not the type associated with leukemias thought to be caused by chemotherapy or benzene [5]. Specifically, chromosome 7 deletion occurs in less than 5% of CML cases and chromosome 5 deletions rare [8]. A search for reported cases in the National Cancer Institute CGAP database shows that there are only 27 cases are found in that database for -5 deletions and 112 cases for -7 deletions (http://cgap.nci.nih.gov/Chromosomes/Mitelman). (It is common that as CML progresses to blast phase and chromosome 7 deletions can be observed there, but -5 are still uncommon [9].)

There are several highly successful treatments for CML. Without treatment, patients with chronic phase CML will progress to the other phases in 3 - 5 years [7]. The risk for transformation was about 3- 4% per year, without modern treatments [10]. CML in blast phase is highly refractory to chemotherapy and so is rapidly fatal. While there have been earlier proposed prognostic factors for CML, such as those proposed by Sokol [7;10], these are no

longer clearly valid since the development of Gleevec. Currently, the adverse prognostic factors for patients include age greater than 60, hemoglobin less than 10, the presence of any blasts in the blood and basophils >5% in the marrow [11]. The latest treatment for CML takes advantage of the molecular changes caused by the *BCR-ABL* translocation and its tyrosine kinase activity [5;7]. The first, and still most commonly used drug is Gleevec (imatinib mesylate) [12;13]. It almost always leads to a complete cytogenetic response, about 70-96% of the time, where Philadelphia chromosome positive cells are no longer detected. The common side effects of Gleevec include nausea, diarrhea, fluid retention (including periorbital edema), bone pain and muscle cramping. Elevation in liver enzymes and dermatologic reactions are less common. There are two other drugs now available that are considered also good first line treatments, which are niotinib and dasatinib [12;14;15]. All three are relatively equivalent and are considered back-ups for each other. The choice of drug depends on the patient and the side-effect profile [13;16]. Mr. Campos had blood count issues with the imatinib and so was switched to dasatinib, without loss of efficacy.

The success of therapy is monitored by quantitative PCR for the *BCR-ABL* fusion, and the best responses are those for persons with a 3 log decrease in transcript over 12 months [17]. Conversely, increasing levels are considered relapse [18]. Also, bone marrows are done to determine cytogenetic responses. Patients are monitored for response at 2, 6, 12 and 18 months, resulting in dose changes or drug changes, as appropriate. By 12 months, there should be a complete cytogenetic response. The transcript level should decrease to below 10% or have better than a partial cytogenetic response. A complete cytogenetic response is defined as no PH-positive metaphases on a bone marrow, while partial is 1-35%; a major response is either complete or partial response, while a minor response is <100% but greater than 35% [13]. For molecular responses, a complete response is no detectable transcripts by QPCR, and a major molecular response is <0.1% or >3-log reduction. For patients failing therapy, mutation analysis is recommended to help direct therapy, e.g., specific tyrosine kinase inhibitors [13;16]

The survival estimate is 96% at 3 years and 82% at 4 years [17;19]. Now, with longer studies, 97% of patients are alive 5-8 years after therapy [13], and 67% at 10 years [11].

If a complete cytogenetic response is not achieved, then a stem cell transplantation is considered [13;20]. The only curative treatment for CML is stem cell or bone marrow transplantation [17]. But, it has been recently projected that long term survival for Gleevec is better than bone marrow or stem cell transplantation generally, which was previously the best long term option for CML [21]. Transplantation from siblings yields a 60% five year survival, and about 50% for unrelated donors. This would now be used for persons who become refractory to Gleevec and clinical trials are exhausted for newer drugs. It also is used for blast phase, and in some persons in accelerated phase who also are refractory to non-transplant treatments.

CML is more common in men than in women, and the median age at diagnosis is 65

years old [7]. It also is more common in African Americans than in Whites.

The causes of CML is essentially unknown, although there are some associations with radiation [6;22]. For example, increase risk has been reported for atomic bomb survivors, radiologists and in persons treated with radiation therapy [7;23-26]. Being overweight may also be a risk factor for CML [27]. Familial patterns for CML do not seem to exist [28].

It is not appropriate to extrapolate risks for all leukemias to any specific leukemia. The cause of CML is likely different than for acute myelogenous leukemia (AML), and appears to be chemically-resistant as an etiology [29]. For example, while cigarette smoking is a known cause of AML, there is only some evidence for increased risk for CML from cigarette smoking [30-32], but other studies are null [27;33]. In contrast, there are many studies about AML, with reported risks are about 1.5-2.0-fold [32;34-41], and a dose-response effect has been reported [27;32;36;40;42;43]. The cytogenetic abnormalities in AML related to smoking are not the type commonly observed in CML, and are not the causative abnormalities[34]. Generally, smoking is not considered a cause of CML. As another example, secondary leukemias following chemotherapy present as AML, not CML. Secondary leukemias occur following some chemotherapy or radiotherapy treatments, such as for Hodgkins lymphoma and breast cancer [44-47]. The secondary leukemias from chemotherapy often are accompanied by abnormal cytogenetics [44;48;49], which are not found in CML [29]. It also is important to note that CML is not considered a leukemia secondary to chemotherapy, and that 9,22 translocations are rare [45;50]. For example, it has been reported that the 9,22 translocation occurs in cases of secondary leukemia from topoisomerase II inhibitors, but this is uncommon [50;51]. There is essentially about 25 cases in the world's literature [50;52]. Because it is uncommon, it is unclear if these really are secondary leukemias, or a *de novo* CML. Generally, for AML versus CML, I am not aware of scientific studies that indicate that either the chromosome -5 or -7 abnormalities are common in CML (see above). Conversely, the 9,22 translocation characteristic for CML is rarely seen in cases of AML, occurring in less than 1% of adult AML [53-55], and these may be persons with previously undetected CML. (The 9,22 translocation is sometimes seen in acute lymphocytic leukemia [55].) Last, CML does not have features of dysplasia, distinguishing it from myelodysplastic syndromes and AML.

Acute leukemia secondary to benzene has been considered to follow a similar mechanism as other secondary leukemias from alkylating agents, because the same chromosomal abnormalities can be found (although not in all studies)[56;57], and so is sometimes more broadly referred to as a secondary leukemia [44;45;58]. The 9,22 Philadelphia chromosome was not reported in these studies. I am aware of one study that reported several cases with the Philadelphia chromosome, but these were mostly in people with prior CML, and there was no relationship with benzene exposure [56].

Charcot-Marie-Tooth (CMT)Syndrome: This is a hereditary disorder of the nervous system, affecting both motor function and sensation [59-61]. The estimated prevalence is about 1 in

2500 people, and is the most common inherited neurological condition. There are actually more than 50 types of CMT, affecting the myelin sheath or the axon, or both. Mutations in more than 29 genes have been identified; mutations in *PMP22*, *GJB1*, *MPZ*, and *MFN2* cause more than 90% of the disease. The pattern is usually autosomal dominant, but autosomal recessive forms also exist. This is a disease that affects peripheral nerves that result in distal muscle atrophy in the legs, decreased reflexes, foot deformities and gait problems. Hands also are involved as the disease progresses. Symptoms start in the first or second decade of life, and are progressive over life. About 20% of patients can have neuropathic pain.

METHODOLOGICAL APPROACHES TO GENERAL CAUSATION AND INDIVIDUAL RISK ASSESSMENT

There are well-established practices for considering if a chemical can cause cancer such as CML. Typical of other physicians and scientists, my initial approach before considering the individual's situation and alleged exposures is to assess if there is a relationship of the alleged exposure to the identified cancer at any level of exposure. This is done by reviewing scientific textbooks and articles, doing computerized literature searches and drawing upon my experience as a researcher, clinician and epidemiologist. The method for the determination of cancer causality is described below. It is important to assess different types of scientific data, relying on the best studies, and even though a researcher might postulate causality (e.g., as might be done through a publication of a case report, an ecological study or a case series), this is different from concluding a causal relationship of exposure to an outcome. Among the types of data that should be evaluated, human epidemiological data is substantially more reliable than laboratory *in vitro* and experimental animal data, assuming the epidemiological and other human studies are of good quality. If there is sufficient epidemiological data to make a conclusion, then experimental animal or other studies are sometimes considered only in the context of understanding biological mechanisms. If there is sufficient reason to consider that the chemical has a potential to cause the type of cancer identified for the individual or a group of individuals (target organ specificity is important), then an individual risk assessment is made to determine the doses reported in the literature that may be associated with an increased cancer risk, and in what settings. The dose, i.e., how much of a carcinogen enters the body, and then reaches the critical organs and targets within the organ, best determines an individual's cancer risk, as carcinogens clearly have a dose-response relationship.

The distinction between dose and exposure must be noted and is important. An individual might be in a room that has a chemical in the air or come into skin contact with a workplace solvent, and so has a potential exposure, but this does necessarily translate into dose, which is the amount of the agent that enters the body. Thus, one must consider that exposure may not be a sufficient marker for dose. Importantly, there is some level below which we can no

longer measure an increased risk, and so any conclusions of cancer causation for exposures below that level are speculative, unsupportable, and at best only hypothetical. (Herein, the concept of increased risk is accompanied by the conventional use of statistics and findings of statistical significance.)

The evaluation of cancer causation, i.e., can an exposure cause cancer, requires examination of different types of data and studies. Published guidelines exist for assessing causality, such as those proposed by Sir Austin Bradford-Hill [62]. These guidelines, others [63-67], and my experience allow me to conceptually develop an opinion about causation. Actually, similar principles espoused by Sir Bradford-Hill were well-applied first in the first Surgeon General's Report on smoking and health, concluding in 1964 that smoking caused lung cancer in men, and distinctions between the original Report and the recent 2014 Report are noted in the latter [67;68]. It has been argued that the Bradford-Hill criteria may be difficult to apply or have limitations [63;69], but there is an appeal for having the best possible framework to guide research agendas and study design [64;65]. Some believe that stating the statistics is sufficient to communicate causality, while not considering the level of risk, or reporting such, is not informative [66]. In some ways, the different models reflect a purely scientific perspective, while others are derived to satisfy public health needs. However, the Bradford-Hill methodology remains the most appropriate and useful for assessing general causation. It also remains the citation and methodology for the International Agency for Research on Cancer (http://monographs.iarc.fr/ENG/Preamble/index.php). As an example for applying a causation analysis, I provide a summary of smoking and lung cancer below.

Table 1 provides the Bradford-Hill criteria. While we remain true to the original writings of Bradford-Hill in many ways, there is a better understanding of how to apply the criteria after 50 years of research, and the following discussion includes several important concepts. As Bradford-Hill wrote, not all criteria are required, but today, we understand that when there is data available for any criteria, then that data cannot be ignored and some criteria are required to be fulfilled when data exists; there are some criteria that if violated would exclude the likelihood of causation, while fulfilling some may not lead to a definitive conclusion of causation without considering other criteria. Among the most important criteria is consistency in the literature, that is, do several well-designed and well-conducted epidemiology studies lead to similar findings in different populations, using different study designs. If there are more than one study available, then consistency must be met, and relying on only one or two studies among many without sufficient justification makes for at best weak support or no support for causality. It should be noted that no single epidemiological study is definitive, and the consideration of a scientific

report is performed in the context of other published studies. A determination of a biological gradient also is important, i.e., do scientific publications show a dose-response relationship, and do those doses occur in the human exposure circumstance of interest. Again, if dose-response relationships have been evaluated and must exist if so, otherwise the criteria is violated and biological plausibility also is lacking. The lack of studying a dose-response relationship, per Bradford-Hill is not required, but without it, then a causality opinion is weakly supported. Another criterion is the strength of association, which allows one to consider if the reported association in an epidemiological study is plausible (e.g., not too high or too low). Originally, Bradford-Hill, following a smoking and lung cancer causation model, considered that the higher the risk estimates, the more likely an association can occur. Now, after 50 years of epidemiological research, we understand that for some exposures and tumor types a high risk estimate is likely not true, for example in the case of a common exposure and a less common cancer as would be the case with low level benzene exposure and acute myeloid leukemia and other hematological malignancies including CML. An evaluation of temporality considers if the exposure sufficiently preceded the cancer effect to allow for latency. Specificity considers if the cancer has other reported causes and if the effect occurs in the identified target organ. Given that lung cancer was a rare disease before smoking, lung cancer and tobacco smoking is an example of specificity. Coherence refers to an evaluation and agreement of different types of scientific data (epidemiological, laboratory animal studies, cell culture models, etc.), and do they provide similar findings that lead to a mechanistic understanding of how the chemical would cause cancer in humans. Human intervention, according to Bradford-Hill are given great weight given that these are experimental situations. Such data might occur, for example, from a medical trial. Analogy looks to see if similar chemicals are known to behave similarly and what is the available scientific data for those chemicals. As an example of consistency within the epidemiological literature, tobacco smoking and lung cancer is used as an example below. In this example, in virtually every study ever done on tobacco smokers, an increased lung cancer

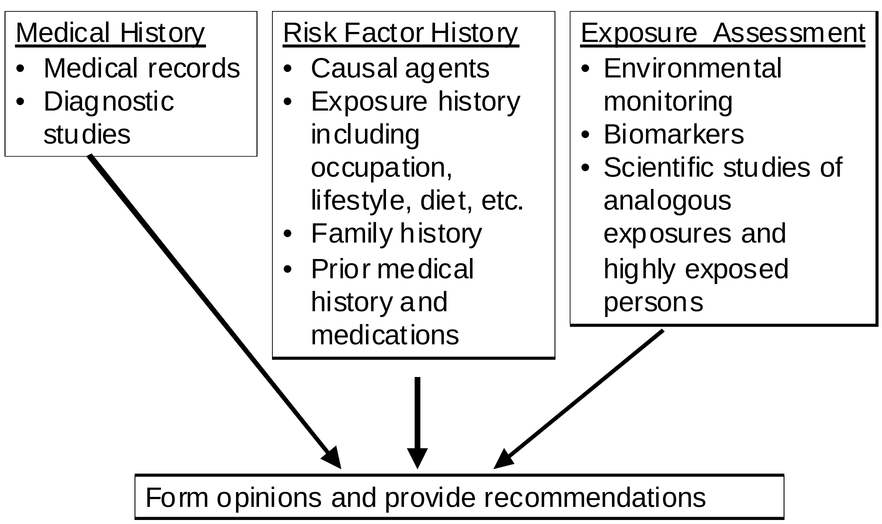
Table 1: Bradford-Hill Criteria for General Causation

- Consistency among epidemiology studies (how many good quality studies say the same thing?)
- Dose-response (does more exposure cause more disease?)
- Timing of exposure (does the cancer come after the exposure and a believable period of time?)
- Strength of Association (are results believable?)
- Specificity (is the disease unique?)
- Biologically plausible (does it make sense?)
- Coherence (is it contradictory to laboratory data?)
- Human interventions (are there reliable clinical studies to consider?)
- Analogous similarities to other toxins

rate or risk is seen. In summary, there is a general consensus for methodologies to consider what causes cancer. I generally follow the criteria set forth about 50 years ago by Sir Austin Bradford-Hill [62]. Some criterions are absolutely required (e.g., consistency and not violating dose-response). Violating some of the principals will preclude the ability to support a causal relationship (e.g., temporality).

Assuming that there is sufficient reason to believe that there is some exposure/dose that might increase cancer risk because of available scientific data, i.e., after evaluating the above criteria, then the degree and circumstances of the exposure from the literature are assessed in relation to the increased risk of the particular cancer found in a worker or group of workers. The individual risk assessment then places this into the context of potential, claimed, and/or documented exposures in an individual or group of individuals. The components of the evaluation to do this are shown in Figure 1. If the exposure level of the individual under consideration is less than that reported in the literature, or the route of exposure is different, then the chemical in question is less likely or unlikely to have caused cancer in the individual. Other unique circumstances also are considered, such as a concurrent disease, comorbidities, and other risk factors (e.g., lifestyle, diet, work place, medication) that might make the individual more or less susceptible. And also if similar exposures occurred from different sources, the relative contribution of each source is considered. Finally, the above information is integrated and a conclusion is made about the probability of causality in a person. Thus, for an individual or small group of individuals, cancer causation can only be done with an understanding of dose placed into context of the scientific literature and a causation analysis.

Figure 1: The Steps for Determining Individual Causation



Another important distinction is the difference between a risk factor and a cause. A risk factor is something that can be established from consistent epidemiology studies with statistical

significance and dose-response relationships, but a confounding factors cannot be ruled out. A cause is decided after considering multiple types of data and the application of the Bradford-Hill criteria that substantially reduces the chances of confounding in epidemiology studies. Importantly, one should not opine a cause without sufficient human evidence. (In some cases following the precautionary principle, organizations such as the International Agency for Research On Cancer makes causal conclusions based on limited human evidence and the presence of mechanistic evidence.)

HOW CANCER DEVELOPS AND THE LATENCY OF CANCER

Cancer, including hematological malignancies, is a multistage process of normal growth, differentiation and development gone awry [70-75]. It is driven by spontaneous (e.g., a defect that happens by mistake during normal replication) and carcinogen-induced genetic and epigenetic events, fueled by signals from the local microenvironment. The genes in the cells of our body are composed of deoxyribonucleic acids (DNA) that serve as a written language that programs a cell's function and provides for the building blocks to make proteins. Carcinogens bind to DNA and cause mutations and gross chromosome changes (e.g., chromosomal deletions, transfers of DNA from one chromosome to another, and chromosomal breaks) and/or alter gene expression (e.g., by affecting the switches for gene transcription). Cells normally replicate, differentiate and provide basic functions that sustain life, and then they die naturally. Some of the control of these genes that allow them to grow and function come from surrounding stromal cells and the microenvironment [74]. Mutated genes and damaged chromosomes in cancer cells, perhaps originating in a cancer stem cell can affect these basic functions, unless naturally existing safety mechanisms prevail. There are redundant DNA repair mechanisms, and cells also can be triggered to die if unrepairable DNA damage exists (a dead cell cannot go on to become cancer). If both of these mechanisms fail, however, cells may begin to replicate uncontrollably, and grow large, ultimately pushing out the normal cells and disturbing organ function. Cancer is therefore a genetic disease comprising many mutations and damaged chromosomes, as well as changes like altered methylation patterns that affect gene expression in clonally expressed cells interacting with a surrounding microenvironment [70;73;76-80]. It is thought that there are stem cells in the microenvironment that contribute to the signals that allow cancer cells to develop. As carcinogens cause cumulative damage, the probability of "initiated" cells to transform into a malignancy increases, the odds of which are increased during repeated rounds of cell replication stimulated by a lack of control in the cancer cell and signals from the surrounding stroma. The primary genes involved in driving the cancer process are proto-oncogenes and tumor suppressor genes. Proto-oncogenes are important to the regulatory mechanisms of growth, cell cycle and terminal differentiation. Activation of proto-oncogenes enhance the probability of neoplastic transformation, which can either be an early or late event. Tumor suppressor genes also code for

products that regulate cell growth and terminal differentiation. However, they have the opposite effect by limiting growth and stimulating terminal differentiation. If inactivated, then the cell may grow uncontrollably or replicate without limits defined only by blood supply and space. Cancer cells also secrete signal proteins that allow for their survival, such as blood vessel formation and allowing for metastases . The micro-environment, namely surrounding stromal cells, create signals and hormones that promote the cancer cell to grow, proliferate and provide the soil for metastases [74;75]. Inflammation and immunity is thought to play a role both for increasing risk and tumor control [81;82]. Emerging research also shows the contribution of infections, considered as the microbiome, to the development of cancer [83].

I have noted that some consider that all hematological malignancies develop from the same type of hematopoietic stem cell, and so a cause of one hematological malignancy can cause any type. This view, though, is not correct.

With the advent of new technologies, it is now recognized that cancer cells and the surrounding cells are perturbed in many ways affecting genes, gene expression, and metabolism, and that these work together to allow for a cancer cell to grow, divide and metastasize [84]. And actually, the most recent thinking about the causes of cancer is that this is a multi-system problem bridging the changes in the cells and microenvironment to the effects of the macroenvironment such as lifestyle and health care policy [85].

People are exposed to carcinogens, mutagens and other toxins every day from many sources. Humans may ingest up to 10,000 different natural pesticides and 1500 mg per day [86;87]. Other sources of mutagens and carcinogens include radiation via sunlight, in our homes, doctors offices, airplanes, etc. There are numerous carcinogens that are ubiquitous in the environment. We are exposed to potential human carcinogens such as benzene, aflatoxins, pesticides, PAHs, N-nitrosamines, heterocyclic amines and other chemicals every day in the diet (e.g., coffee, vegetables, smoked meats, and fish) [88]. Cooking produces 2000 mg/day mutagens, e.g., 1.8 ug of heterocyclic amines [88;89]. Human cells have 150,000+ DNA adducts from chemicals produced in our bodies.

Cancer is mostly a disease of aging. This is likely to be due to the redundant and protective mechanisms present in humans, e.g., metabolism, DNA repair and programmed cell death. While the DNA in our cells are constantly being exposed and affected by mutagens from birth, and before, most cancers do not develop until adulthood, and mostly much later. It is remarkable that we do not all get cancer in childhood, if the presence of mutations, or single molecules were sufficient to cause cancer. Also, it is remarkable that persons we treat with chemotherapy or radiotherapy do not all get cancer. The fact that not everyone gets cancer at early ages also is consistent with a threshold effect for accumulated genetic damage (e.g., that one molecule cannot cause cancer, and that there needs to be enough exposure to cause multiple genetic abnormalities).

Given that cancer develops from multiple genetic and epigenetic defects in the cancer cells plus support from the surrounding microenvironment, and that humans have redundant repair mechanism to preserve normal cell function, there is likely a threshold level for carcinogenesis. Clearly, cancer is a complex process that is not affected by a single molecule, as has been previously thought, contributed to by both the micro- and macroenvironment [85]. For example, as dose increases, there is increased risk to overwhelm the repair mechanisms, changes in the microenvironment and accumulate pro-oncogenic damage in cancer cells. In the regulatory arena, however, some risk assessment models follow the precautionary principle, assume that there is no threshold for genotoxic dose and cancer effect, while there is one for epigenetic effects. However, the determination of genotoxicity and epigenetic alterations is generally determined by experimental studies with unclear relevance to humans. There are no equivalent human models to conclude that a human carcinogen only works by one mechanism or the other.

Regulatory and Review Agency Classifications: Several review and regulatory agencies have considered the carcinogenic potential for chemicals cited in the complaint for this case. It is important to realize that regulatory and review processes, and the conclusions derived therein, are not applicable to the process of directly assessing past and future risk for individuals or groups of individuals. These agencies are classifying agents in order to prioritize which potential exposures should be considered for risk assessments and regulatory control. It also is important to understand that these agencies consider population cancer risks (e.g., in thousands and millions of people) and do not provide conclusions regarding individual cancer risks (or for small groups of individuals). Their conclusions are focused on protecting public health, i.e., to acknowledge that there are limitations in the scientific data and some risks might not be measurable. Their methods lead to an interpretation of data in ways that err on the side of caution and assume worse risk than can exist. While this is an important process to protect humans before we learn whether a chemical causes cancer in people, these agency methods and findings are not appropriate to support a conclusion of cancer causation in a particular individual, or to predict risk in particular individuals, or to conclude whether the chemical is carcinogenic in humans at all. Moreover, a conclusion of possible or probable carcinogenic potential for one type of cancer in a target organ does not imply that the chemical can cause cancer in other organs.

When reviewing the preambles or methodologies for all the regulatory and review agencies, it is clear that they instruct the reader to not infer individual causation from the classification assessments. In fact, they also make it clear that their classification scheme, for example labeling a chemical exposure as probable or possible human carcinogen, should not be equated with the conclusion that the exposure actually is a human carcinogen. For example, ATSDR indicates that their minimal risk levels serve as a "screening tool to help public health professionals decide where to look more closely" (http://www.atsdr.cdc.gov/mrls/index.asp). The International Agency for Research on Cancer writes: "The Monographs are used by national

and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions." (http://monographs.iarc.fr/ENG/Preamble/index.php). The EPA, in its IRIS assessment writes: "In general IRIS values cannot be validly used to accurately predict the incidence of human disease or the type of effects that chemical exposures have on humans. This is due to the numerous uncertainties involved in risk assessment, including those associated with extrapolations from animal data to humans and from high experimental doses to lower environmental exposures. The organs affected and the type of adverse effect resulting from chemical exposure may differ between study animals and humans. In addition, many factors besides exposure to a chemical influence the occurrence and extent of human disease." The National Toxicology Program adopts the same language (http://ntp.niehs.nih.gov/index.cfm?objectid=03CA6383-9766-1F64-6637241FE0114FE9).

IARC classifies benzene as a known cause of human cancer, but this is for acute myelogenous leukemia, and not for CML. IARC does not consider mineral spirits to be a possible, probable or known human carcinogen.

Target organ specificity: With only a few possible exceptions, chemicals exert their carcinogenic effect specifically to only one or a few organs. Target organ specificity is common and biologically plausible given that cancer arises from the combination of the abnormal clonal cells and the microenvironment around those cells. This also applies to hematological malignancies. Just as our organs are not interchangeable, the types of cancers that arise from them are different. Exposure routes allow for greater or lesser exposure at the cellular level in the target organ (i.e., different blood flow or blockage of exposure by the blood-brain barrier). Different tissues express different metabolizing proteins such as cytochrome P450s, which are "intended" by evolution to be protective and aid excretion. Different tissues have different DNA damage, repair and programmed cell death capacities. The microenvironment from adjacent cells provides signaling molecules and other hormones. Organs have different clearance mechanisms. There are some chemicals that one would predict would be multiorgan carcinogens in humans, but are not. These include phenobarbital and caffeine. If a particular chemical exposure were a multi-organ carcinogen, then these exposures would still have a consistent effect within a species. For humans, we would find consistent effects across studies, namely that all cancer-combined incidence should be increased, and we should see replication of at least some individual cancer types across studies. For any of the chemicals at issue in this case, as listed below, there is insufficient evidence to indicate that these are multi-organ carcinogens, and almost all lack sufficient evidence for cancer risk in humans

LUNG CANCER AS AN EXAMPLE OF A KNOWN HUMAN CARCINOGEN

Lung cancer is the leading cause of cancer-related death in the United States, and the second most commonly diagnosed in men and women [90]. The risk of lung cancer from smoking is well documented, as described below. It is instructive to consider the scientific data for smoking and lung cancer, to place into context the allegation by plaintiff's experts. The application of the Bradford-Hill criteria is and applicable to the evaluation of other chemicals. While this analysis focuses on smoking and lung cancer, a similar analysis for cigarette smoking and acute myelogenous leukemia also would demonstrate causality, and for occupational exposure to benzene and acute myelogenous leukemia. However, a causation analysis for CML would fail for a causation with benzene exposure.

There were an estimated 228,190 new lung cancer cases, and 159,480 lung cancer deaths in 2013 [91]. The incidence of lung cancer has been rising dramatically over other cancers, due to tobacco smoking (see below), although the rate has been declining recently (Figure 2; reproduced [90]).

The most common histological types of lung cancer are grouped together as a non-small cell lung cancer, which is further divided into squamous cell cancer and adenocarcinoma. Some people can have a mixed histology, and some may be classified simply as large cell. A less common type is small cell cancer. Until recently, squamous cell cancers were more common than adenocarcinomas in men, but this has changed recently, and adenocarcinomas are more common [92]. This is thought to be due to a change in types of cigarettes smoked, namely filtered light cigarettes. Lower tar cigarettes have been recently considered as a cause for the increased rates of adenocarcinomas [67].

Tobacco smoking is among the best examples of a human carcinogen, and is very well-documented to cause lung cancer [92;93]. In 1950, Doll and Hill [94], and Wynder and Graham [95] both reported the extremely high incidence of smoking in lung cancer patients. In fact, lung cancer was a rare disease before smoking [94]. If one is to use almost any method to assess causality, such as that proposed in the first Surgeon General's Report [96], and later articulated in more detail by Sir Austin Bradford Hill [62], then clearly the use of tobacco products causes cancer. The process for the causation analysis has been recently reviewed [67]. This conclusion comes from substantial epidemiology, laboratory animal and *in vitro* studies. It accounts for about 90% of lung cancer cases [97]. Even low levels of cigarette smoking increases lung cancer risk [98]. A summary of selected studies is shown in Table 2. Tobacco smoke contains more than 100 carcinogens and mutagens, many of which are classified as carcinogens based upon human and animal studies , the latter of which include target organ specificity. It is estimated that 20% of all cancers worldwide are attributed to smoking [99]. Smoke constituents include

PAHs, arsenic, benzene, dioxins, nitrosamines, aromatic amines, vinyl chloride, and chromium [100-103]. A dose-response relationship for cigarette smoking and lung cancer has been established in cohort studies of both men and women (Table 2). These studies show remarkable consistency. Both daily smoking amounts and duration of smoking are important contributors to risk in various models, although there are some disagreements about whether smoking per day or duration is more important [104;105]. An earlier age at initiation is a separate lung cancer risk

Figure 2: Cancer Mortality Trends

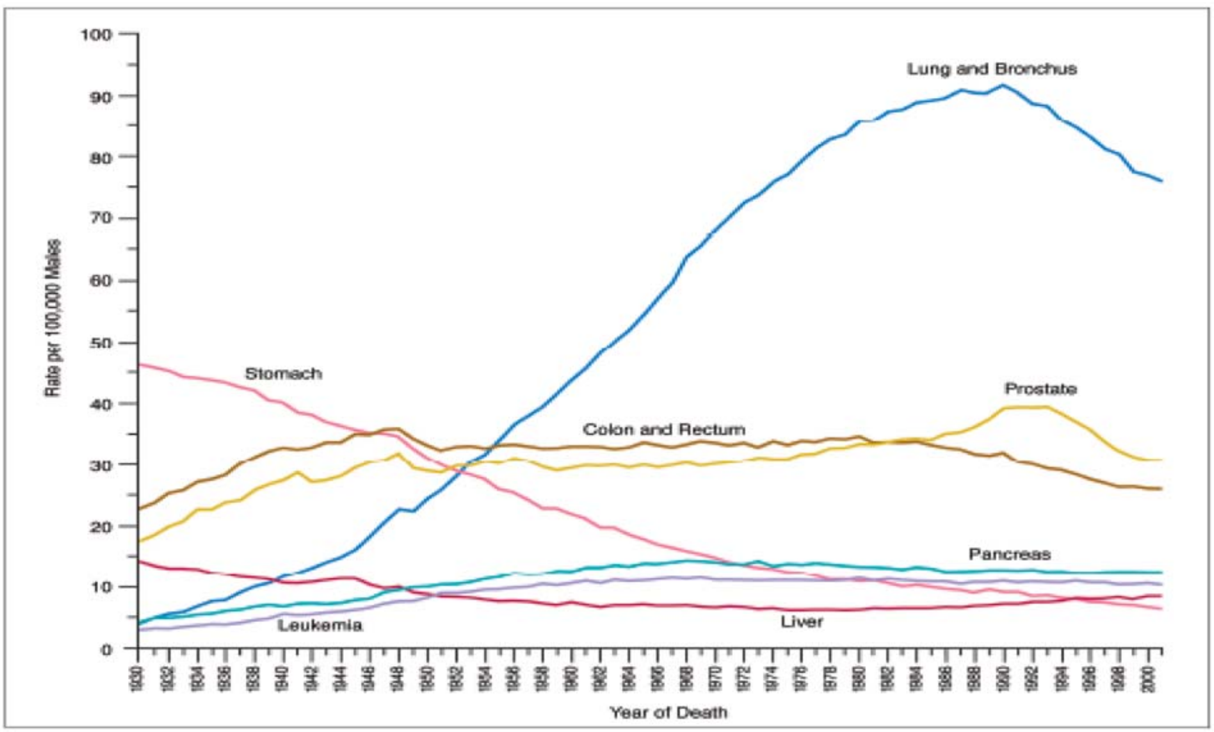


FIGURE 4 Annual Age-adjusted Cancer Death Rates* Among Males for Selected Cancer Types, US, 1930 to 2001.
*Rates are age-adjusted to the 2000 US standard population.
Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the lung and bronchus, colon and rectum, and liver are affected by these changes.
Source: US Mortality Public Use Data Tapes, 1960 to 2001, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

factor [106-108]. Zang and Wynder had proposed an estimate of cumulative "tar" exposure by determining all brands used for different periods of life, the quantity per day and the milligram yields were calculated per the FTC method [109]. The reported effect of how deeply someone inhales also has been associated with an increased risk [107;108]. In a cohort of smokers with lung disease (chronic airway obstruction), about 33% of middle-aged smokers developed lung cancer after 14.5 years [110]. There is data to show that smoking unfiltered cigarettes had higher risks compared with smoking other types of cigarettes. Analyses of large cohort studies support

Table 2
Selected Lung Cancer and Smoking Studies – Consistency of Association

Cohort	**Number of subjects**	**Positive lung cancer association?**	**Dose-Response (risk estimate)**
British Doctors	34439	Yes	Yes (15)
ACS-25 State Study [111;112]	120000 men 619925 women	Yes Yes	Yes (11)
U.S. Veterans [113]	293,958	Yes	Yes (11)
Japanese Study [114]	265000	Yes	Yes (5)
ACS – 9 State Study [115]	187,783	Yes	Yes (11)
Canadian Veterans [116]	78000	Yes	Yes (NA)
Swedish Study [116]	25,444	Yes	Yes (NA)
California Study [117]	68,153	Yes	Yes (8)
MRFIT [118]	12,866	Yes	Yes (7)
Iowa Women's Health Study [119]	41,843	Yes	Yes (10)
Norwegian Study [120]	68,825	Yes	Yes (16)

this conclusion [122]. In studies of filtered versus nonfiltered cigarettes, smokers of filtered cigarettes had a decreased lung cancer risk by 30% in a French study of 1,057 lung cancer cases and 1,503 controls [123], a 2-fold lower risk in a Philadelphia study [124] and a 4-fold decrease for women in a Spanish study . Wynder and Stellman [125] reported that in 684 cases and 9,547 controls, there was a reduced risk for smokers of nonfilters cigarettes for ten years or more, although the results were not statistically significant. However, when they later reported data for 1,242 lung cancer cases compared to 2,300 controls, and accounted for increasing smoking per day after switching to lower "tar" cigarettes, they found that lung cancer risk was not reduced, and even increased in the highest levels of compensation [126]. Other studies also have reported a reduced risk for filtered cigarettes [127;128], but dose-response relationships for persons mixing their brands was harder to demonstrate [128;129]. There are some studies, however, which do not support a decreased risk for filtered cigarettes. In a population-based case-control

study, when amount of smoking was considered, there was no benefit to the filtered cigarettes [130]. Data pooled from four cohorts failed to show a statistically significant benefit for filtered cigarettes and lung cancer risk, even among different levels of smoking [131], as did another large cohort of 79,946 members of Kaiser Permanente (RR=1.03 for men and 0.65 for women, neither statistically significant), although women who used filtered cigarettes for more than 20 years had a risk of 0.36 (95%CI=0.18, 0.75) [132]. Thus, while there are a significant number of studies to indicate that smoking unfiltered cigarettes is more risky for lung cancer, this conclusion is tempered by contrasting studies. Filtered cigarettes compared to nonfiltered cigarettes are more closely associated with adenocarcinomas rather than squamous cell cancers [133], although this observation is more strongly related to women smokers [134].

Corroborating the increased risk of smoking for lung cancer are clinical trials that show that quitting reduces the incidence of lung cancer [110]. Large cohort and case-control studies also report the benefits of quitting [122]. Reducing how much someone smokes per day decreases the risk somewhat [135].

Environmental tobacco smoke (ETS), also termed passive smoking or exposure to second-hand smoke, has been estimated to cause 2,600 to 7,400 lung cancer deaths per year among non-smokers in the U.S., according to a review of 9 studies of lung cancer mortality . The initial evidence linking ETS with increased risks for lung cancer came from studies in Japan and other countries in which smoking among women is rare. The conclusion that ETS is a cause of lung cancer has been opined by several reviewers and persons conducting meta-analysis [136-140]. This is an example of how it is possible to document increased risks from low level exposure, when it occurs. In many studies, the risk of lung cancer among non-smoking women was evaluated in relation to the presence/absence of a husband who smokes. For example, Fontham, et. al., [141] reported an odds ratio of 1.5 for the association of lung cancer among lifetime non-smoking women who lived with a spouse who smoked. Janerich et al.[142] found no association with ETS in adulthood but an odds ratio of 2.0 for high levels of household tobacco smoke in childhood. Stockwell et al.[143] compared 210 women with lung cancer who were lifetime non-smokers with 301 controls assembled by random digit dialing. The maximum effect detected was an odds ratio of 2.4 (95% CI 1.1-5.3) for >40 smoke-years of exposure (with a p-value=0.004 for trend). Numerous other studies support the conclusion that ETS exposure increases lung cancer risk [136;143-145]. A recent review of 44 such studies revealed that the relative risk for lung cancer among non-smokers is between 1.16 and 1.24 for women who have a husband who smokes, relative to non-smokers whose husbands are also non-smokers [146]. Examining studies that use cotinine to classify ETS exposures, Tweedie and Mengersen used a meta-analysis approach and concluded that ETS risk was 1.17 (95%CI=1.06, 1.28) [144].

In summary, if one assesses the causation criteria by Bradford-Hill to smoking and lung cancer, every criterion is fulfilled, even at low dose exposures such as ETS . As stated above, a similar analysis could be done for cigarette smoking and acute myelogenous leukemia, as is true

for benzene and acute myelogenous leukemia, leading to a causal conclusion. However, the risk for causally relating benzene to leukemia is clearly related to dose. A similar analysis for CML and smoking, and also benzene, would demonstrate insufficient data to conclude causation.

MINERAL SPIRITS

The Safety-Kleen products used by Mr. Campos are essentially mineral spirits. Mineral spirits is a generic term for petroleum solvents, which is a complex mixture of straight and branched chained carbon compounds (aliphatic hydrocarbon compounds). There can be several Chemical Abstract Service (CAS) numbers associated with mineral spirits [147]. It is similar to, and is sometimes used synonymously with Stoddard solvent, naptha (although naphtha also can be composed of aromatic hydrocarbons), white spirits and benzine. Basically, mineral spirits and related chemicals are distilled from petroleum, and so it is a refined petroleum product. Because of the concern of potential contamination with benzene, contaminant levels have been controlled for decades, including the 1970's, and the benzene content is usually <0.1%, and typically less than 0.005% [147;148]. The Safety-Kleen 105 virgin and recycled solvents have been studied, and the benzene levels are trivial, well-below levels of federal reporting requirements on MSDS'.

Mineral spirits are widely used; it is estimated that more than 75,000 workers use mineral spirits daily [149]. With such large numbers of workers, the potential toxicity of use has been well-studied. If there were some risk of CML, or even acute leukemia, this would be known. ATSDR, in their 1995 Toxicological Profile for mineral spirits does not indicate that there is a benzene exposure related to mineral spirits [150]. ACGIH does not consider that mineral spirits contain a significant amount of benzene, citing only a single case report of a worker with aplastic anemia [151]. IARC does not classify mineral spirits as a human carcinogen. The toxicology of mineral spirits has been extensively studied [147]. Mineral spirits are not genotoxic in the laboratory, and there are no genotoxicity studies in humans that I am aware of. Mineral spirits are generally not tumorigenic in experimental animal studies, although one model uniquely is associated with adrenal tumors [147;152]. Studies of workers using mineral spirits are appropriate studies to consider for the alleged CML risk in Mr. Campos, because these typically have some low level content of benzene, and none that I am aware of report an increased risk of CML. While plaintiff's experts opine that benzene is a relevant discussion point for assessing Mr. Campo's workplace risk, actually, he worked with mineral spirits and not benzene. There is no evidence that the Safety-Kleen provided to Mr. Campos' workplace was different than any other virgin mineral spirits, and in fact, there is testing for Safety-Kleen 105 shows benzene content at trivial levels.

It is my understanding that the Safety-Kleen 105 solvent in Puerto Rico was only virgin solvent and not recycled solvent. However, even if Mr. Campos worked with the recycled solvent, my opinions would not change given the trivial amounts of benzene that occur in the

recycled solvent.

Benzene air sampling around parts washers indicate exposure levels below permissible limit and generally at background, especially after several days of use. For example, the NMAS 1995 study sampled 15 customer locations using the parts washers, including facilities that repaired automobiles, trucks, trains and motorcycles. Sampling also was done at service facilities and industrial production sites. All the air sampling in the customer sites were below permissible limits and most were not-detected. Levels decrease over time as the benzene is volatile and levels decrease rapidly within hours of use, e.g., Brinkman and Blair 1990 report: Volatile Solvent Evaporation From An Operating Parts Washer. Published research articles are in agreement for sampling of parts washer mineral spirits, air levels and how levels rapidly drop [153-155]. NIOSH also has evaluated several sites that use Safety-Kleen and elevated benzene levels were not reported, nor was benzene even expressed as a concern.

BENZENE

It has been alleged that benzene exposure in this case caused Mr. Campos to develop CML. However, Mr. Campos worked with mineral spirits, and not benzene, or a product with significant amounts of benzene. For this report, given that plaintiff's experts somehow take importance to trivial benzene content of mineral spirits, ignoring studies of mechanics or similarly exposed workers, and studies of mineral spirits and leukemia risk as discussed below, I will consider risks of benzene exposure for CML. Benzene exposures in the workplace have been extensively studied, and it was recognized early that benzene was some types of leukemia (but not lymphoma). There are numerous epidemiological studies to conclude that sufficient exposure to benzene is a risk factor for acute myelogenous leukemia (AML) [156]. However, it is important to note that there is a clear dose-response effect [157-160], which results in regulatory agencies making the determination for permissible level of workplace exposure. So, as plaintiff's experts' erroneously claim relevance that benzene is a cause of AML to opine that benzene is a cause of CML, they provide a misleading opinion because Mr. Campos was not exposed to enough benzene to cause AML, and benzene is not a known cause of CML. Thus, the discussion of benzene exposure and AML generally to support a general causation opinion for benzene an CML irrelevant and misleading. More so, to claim a level of exposure that would lead to the development of any disease in Mr. Campos, there would need to evidence that there is some level of exposure that was exceeded permissible occupational limits, and also that there were some workplace activities that exceeded those of mechanics to somehow claim that the large number of scientific studies about benzene exposure for mechanics and similar workers would not be relevant. Because, worker studies for mechanics and similarly exposed workers, as indicated below, do not establish an increased risk for CML.

Positive studies for benzene exposure and AML indicate that there is a specific level of exposure that is needed before the risk of AML becomes statistically significant. The levels of exposure to benzene in workers with potentially high exposure to benzene have been documented for industries with increased AML risk, along with the variables that would modify the exposure levels; in some series, the levels for AML need to be equivalent to at least 40 ppm-years, some report risks at 200 ppm-years. I note that some studies report an increased leukemia risk at 8-10 ppm-years, although a recent re-analysis as part of a pooled study of several refineries did not find an increased AML risk (see below) [161-166]. It should be noted that actual benzene exposures have not been measured for Mr. Campos, and there is no evidence for the level of a potential exposure from one particular product or another.

The potential for benzene exposure in many work-places has been well-documented, and there is a wide range of exposures depending on the occupation [159;167;168]. There is frequent background exposure to benzene in the general population [159;169-171]. This could be from tobacco smoke, diet, car exhaust, and gasoline filling stations. However, if benzene at low doses, e.g., at background, substantially contributes to leukemia risk, then AML or CML would be common diseases. This is not the case.

There are different ways to consider Mr. Campos' actual exposure, such as considering published studies for air monitoring and biomarker studies. Biomarker studies for benzene exposure are better than environmental monitoring or personal air sampling because they provide estimates of exposure by all routes, namely both inhalation and dermal. For example, service station attendants, analogous or worse than the exposures assumed for Mr. Campos, increase their mean breath concentrations to benzene, xylene and toluene over background levels, but being above background cannot be equated to having increased risk for disease [172;173]. For this discussion, t should be noted that Mr. Campos was a repairman who did not pump gasoline or work to repair cars, both of which would have a higher usage of product and exposure to gasoline. There are different markers that one can use for benzene exposure, namely benzene levels in blood or urine, the *S*-phenylmercapturic acid (SPMA) in urine and the *t*,*t*-muconic acid in urine (TTMA). Each has advantages and limitations [168]. Benzene levels are the direct assessment of the actual unmetabolized exposure but can vary among people based on time since exposure and metabolic rates. The SPMA and TTMA reflect exposure over a longer period of time (e.g., the half-life of SPMA is 9 hours), but both can be influenced by metabolic rates as well. The SPMA is considered more specific but there is a larger database for TTMA, which can be confounded by diet. The American Conference of Governmental Industrial Hygienists recommends monitoring with SPMA or TTMA, and have published biological exposure indexes (BEI) of 25 ug/g creatinine and 500 ug/g creatinine, respectively, for end of shift levels [174]. There are many biomarker studies that consider gas station attendants and mechanics, and some consider levels in the context of smoking. Reported biomarker levels can vary by laboratory method, and are less reliable at lower levels of exposure [149;175]. Generally, exposures for the workers are higher than nonworkers, but cigarette smoking contributes largely to levels; general

population smokers can have higher levels than workers, but this can vary by the country (some countries still allow high levels of benzene in gasoline), the amount of exposure, the presence of regulation for exposure, and the amount of smoking. Several studies report higher levels for both work and smokers, but all levels are below the ACGIH BEI [174;176-178]. Among the best studies is by Fustinoni, et. al., from Italy where 78 gas station attendants were compared to 58 referents, and smoking status was reported, where the authors reported the validation of their method [175;179]. They also reported a correlation with urine cotinine. The SPMA median levels in referent nonsmokers and smokers were 4.1 and 8.0 (ug/l) and for gasoline attendants they were 5.8 and 7.5 (ug/l), respectively (levels were not corrected for creatinine). Similar results were reported by Manini, et al, including a correlation with urine cotinine [180]. Some studies report results that SPMA and TTMA are higher in exposed workers compared to controls, but smoking was not considered [181-183]. One study in Thailand indicated that gasoline workers might have levels higher TTMA than the ACGIH BEI, but smoking was not assessed and could be high in that part of the world, and an earlier publication from the same group reported levels in men to be similar [182;184]. In summary, while gas station attendants and mechanics might have higher biomarker levels than the general population, they do not have exposures above permissible occupational limits and have levels similar to smokers, where we know that smoking does not increase the risk of CML.

Chronic myelogenous leukemia and benzene risk: Most of the studies cited above only consider benzene and acute leukemia risk, or leukemia risk in general. There also has been study for CML, and the available literature does not support the causal opinion that benzene can cause CML at some dose [170;185-187]. In a review of 10 studies, only 2 were reported positive [185]. Among studies of highly exposed workers, in the series of publications from China, no statistical increase could be found[188-190]. Also, the shoe workers in Turkey were not reported to have an increased risk of CML, including for those with high levels of exposure and pancytopenia [191-193]. For the Rinsky rubber worker studies, CML was not increased; in that study, there were only three reported cases, two of which worked less than 1 month and one had an ICD code for acute leukemia [163]. Other rubber worker studies are null for CML [185;194-196]. Another study of leukemia that reported levels of benzene exposure do not find increased numbers of CML patients [197]. For the petroleum industry, where CML also was studied, null results has been reported [185;198-207], or inferred as null [208;209]. Recently, Schnatter and colleagues conducted a pooled analysis of 3 refinery worker cohorts and did not find an increased risk for CML; there was one analysis that was positive at lower levels of exposure but not higher, and was inconsistent with the other findings in the study [160]. Workers in the chemical industry and other industries with benzene exposure were null, or inferred as null for CML [210-214].

Consideration of other occupations for exposure to benzene at low levels, such as printers, painters and mechanics are helpful for understanding Mr. Campos' risks. These occupations are not considered to be at increased risk for CML, or even leukemia generally;

most or all studies within groups are null that I am aware of [215-219], with only two exceptions [216;220].

A large meta-analysis by Wong and Raabe in 1995, based on 208,741 petroleum workers from the U.S. and Canada, with 4,665,361 person years, 56,441 deaths, and 19 cohorts, found that the SMR for AML was only 0.89 (95% CI= 0.0.68, 1.15) [221]. Among the 19 cohorts reported, none had a statistically increased incidence of CML. Combined in different ways by geography, the meta-analysis did not indicate an increased risk, statistically significant or otherwise.

Vlaanderen and colleagues recently published a meta-analysis for benzene-exposed workers and CML. Their conclusion was "Although limited by low statistical power, the current meta-analysis provides support for a possible association of occupational exposure to benzene and the risk of CML.[22]. Thus, in the context of individual risk assessment, this paper refutes a positive causation opinion. The authors analyzed the data in different ways in order to provide importance to different approaches, and what the considered as the most reliable provided null results. They wrote: "The highest study quality stratum for AML significance and exposure quality showed an elevated but non-significant increased mRR (1.40; 95% CI: 0.86–2.27, and 1.68; 95% CI: 0.74–3.84, respectively)." The only positive analysis actually was for more recent studies, which is the inverse for what would be expected with workers having a higher exposure in the past. (The authors, though, also noted that these would have more certain diagnoses.) Importantly, for all the 17 studies cited by the authors, none were statistically significant.

Other meta-analyses over the last several years also are null, and use either different methodologies, including an assessment of case-control studies, and/or include additional studies [158].

I am aware of a review article published in 2006 by Myron Mehlman [222]. This publication is essentially an incomplete review of the literature that takes great weight in noting only that CML cases are reported in cohorts without consideration to statistics, similar to inappropriately relying on case-reports for causation opinions. There are a few statistically significant reported results in the review, but virtually all of these do not even study CML, or were falsely cited as being statistically significant. The Mehlman review was specifically discussed by the Vlaandaren, et. al., researchers [22], who discounted the Mehlman conclusions saying that no data synthesis was conducted. Clearly, if CML were to be associated with benzene exposure, given all the study of benzene and leukemia, it would have been identified and CML would not be such a rare disease.

PLAINTIFF'S EXPERTS' OPINIONS

Su-Jung Tsai (12/10/13): Dr. Tsai opines that Mr. Campos was exposed to perchloroethylene above occupational limits by inferring an odor threshold from mineral spirits. This is not an accepted practice for assessing either an STEL or 8 hour TWA. She provides no data for an association for perchloroethylene and CML generally, or specifically at the levels of exposure she guesses at. More so, I am not aware that perchloroethylene is an issue in this case, or even present in the virgin Safety-Kleen 105 that probably used by Mr. Campos. For benzene, there is no specific assessment of exposure, and Dr. Tsai erroneously cites to the Vlaanderen meta-analysis of CML to support her opinion; the authors stated that their analysis provides support for only a possible association and that their best evidence provided a null result [22].

Arthur Frank (12/13/13): Dr. Frank opines that Mr. Campos developed CML from his workplace. There is no discussion of the scientific literature and no report of a methodology. He cites only to Mehlman [222], which, is not an authoritative work and is in contrast to that of researchers in the field, as cited above via several meta-analyses. Importantly, Dr. Mehlman published his opinions in 2006, and so there was no benefit to the more recent studies a discussed above. The weak reliance on this publication is discussed above.

Dr. Frank apparently confuses CML with other forms of leukemia and apparently does not recognize the distinct features of the disease and etiologies.

Dr. Frank also opines that cigarette smoking contributed to Mr. Campos developing CML, although this is inconsistent with current scientific opinion. However, if Dr. Frank were not wrong in his opinion, he would have to conclude that smoking was a major risk factor, and he would not be able to say that Mr. Campos would not have developed CML, but for the alleged work-place exposures. Dr. Frank claims that smoking would lead to a small benzene exposure, but how he makes this comparison to the workplace is unclear and fails to consider smoking behavior and direct inhalation of cigarette smoke carcinogens.

David Goldsmith (12/13/13): Dr. Goldsmith provides a general and specific causation opinion for benzene and “mineral oils/solvents” exposure and CML. Like Dr. Frank, he confuses the leukemias and considers them all the same. He cites to IARC, who never claims a causal relationship for benzene to CML. His discussion of “mineral oils/solvents” is somewhat puzzling as these are different chemical mixtures with different toxicities. Dr. Goldsmith cites to Mehlman, which, as indicated above are not authoritative by any means, and provide contrary opinions to experts in the field. He also cites to a publication by Polychronakas, actually, makes no statements about benzene exposure and CML, and so it is puzzling why Dr. Goldsmith relies upon that work.

Dr. Goldsmith cites to specific publications that do not support his opinions or he miscites them. For example, he cited to the Schnatter 2012 publication [160] as supporting his opinion, which it does not. The same is true for the study by Yin, 1996 [190], although in this case, Dr. Kaufman did indicate that the study was null. In sum, the only research study cited by him that was statistically significant was the study by Adekoke, et al. 2003 [216], which

contradicts the literature and fails to establish consistency. There were no studies cited by him about mineral spirits.

Dr. Goldsmith does not cite to any methodology for formulating his opinions.

Melvin Kopstein (12/13/13): Dr. Kopstein provides an exposure assessment. He does this based on indirect evidence and does not cite to studies with actual measurements, as indicated above. There are also issues with using greatly exaggerated benzene content levels in virgin SK105. As a result, the alleged exposures are grossly inconsistent with studies that I cite above, both for exposure and for leukemia risk generally. Importantly, Dr. Kopstein provides only an exposure estimate for peak exposures and not cumulative exposure exceeding OSHA TWA limits. This is insufficient evidence to rely upon for a specific causation method. He states that Mr. Campos cumulative exposure was in excess of 2-3 ppm years, which is insufficient to increase the risk of leukemia of any type at that level.

CONCLUSIONS

1. Mr. Campos was diagnosed with chronic myelogenous leukemia. I have no particular reason to question the diagnosis. There are no unusual aspects of Mr. Campos' disease to implicate an unusual etiology.

2. The causes of CML are essentially unknown, and so virtually all patients with CML do not have identifiable risk factors and a cause is never understood. However, simply because there are no identifiable risk factors, it is not appropriate to conclude that the workplace caused the CML because "something must have done it".

3. There are many types of leukemia. It is inappropriate to consider them all the same in the context of risk.

4. Mr. Campos was a precision tool technician, which would have had activities similar to mechanics. There are many studies of mechanics and gas station attendants that can be considered to understand his workplace risks as an analogy. The literature does not implicate an increased risk for CML for these types of workers or workers who work with similar solvents and degreasers.

5. The allegation in this case is that Mr. Campos developed CML as a result of working with Safety-Kleen 105. This Safety-Kleen product is essentially mineral spirits. Many workers use mineral spirits; as an exposure there are scientific studies to consider. Mineral spirits are not considered a cause of CML. Plaintiff's experts make opinions about benzene, but Mr. Campos did not work with benzene. Rather, he worked with mineral spirits. The benzene content of mineral spirits is well-known and is trivial. It is

inappropriate to focus on benzene exposure for workers who work with mineral spirits, even if benzene was a cause of CML.

6. Mr. Campos had a trivial level of benzene exposure that was likely not above background and likely not above permissible limits, based on available studies. Benzene and leukemia risks have been extensively studied. If benzene was a cause of CML, we would know this. If benzene caused CML, it would not be a rare disease. After almost 50 years of study, contemporaneous researchers do not conclude that benzene is a cause of CML.

7. I generally follow Bradford-Hill criteria for general causation to consider levels of exposure and workplace activities for Mr. Campos, and for specific causation methodology as described herein. Understanding exposure within a general and specific causation are both very important and plaintiff's experts make wild assumptions. It is my opinion that Mr. Campos did not develop CML as a result of working at Makita or elsewhere where Safety-Kleen parts washers were used.

8. Plaintiff's expert, Dr. Kopstein, provides an exposure estimate that is fundamentally flawed, wrong and inconsistent with scientific studies. And given the lack of support to conclude that benzene is a cause of CML, the alleged exposures actually are irrelevant.

9. I have reviewed the plaintiff's experts' reports. I fail to discern a scientifically acceptable methodology for assessing individual or general causation. I note the lack of studies cited by them that support their opinion. They want to rely on studies of leukemia generally, but this is inappropriate and flawed. They fail to consider dose, even that alleged by Dr. Kopstein, in their opinions; not a single study is cited that show that CML risk is increased at the levels of exposure opined by Dr. Kopstein.

10. The above opinions I hold to a reasonable degree of medical and scientific certainty. If you have additional questions, I will address those. If additional documents or materials are brought to my attention, then I reserve the right to modify or supplement my opinions.

Sincerely,

Peter G. Shields, M.D.
Professor of Medicine and Oncology

LITERATURE CITATIONS

1. Siegel,R., Naishadham,D., and Jemal,A. (2013) Cancer statistics, 2013. *CA Cancer J Clin.*, **63**, 11-30.

2. Spivak,J.L., Barosi,G., Tognoni,G., Barbui,T., Finazzi,G., Marchioli,R., and Marchetti,M. (2003) Chronic myeloproliferative disorders. *Hematology.(Am Soc.Hematol.Educ.Program.)*,200-224.

3. De,K.K. and Cools,J. (2006) Chronic myeloproliferative disorders: a tyrosine kinase tale. *Leukemia*, **20**, 200-205.

4. Michiels,J.J., De,R.H., Berneman,Z., Van,B.D., Hebeda,K., Lam,K., and Schroyens,W. (2006) The 2001 World Health Organization and updated European clinical and pathological criteria for the diagnosis, classification, and staging of the Philadelphia chromosome-negative chronic myeloproliferative disorders. *Semin.Thromb.Hemost.*, **32**, 307-340.

5. Mauro,M.J. and Deininger,M.W. (2006) Chronic myeloid leukemia in 2006: a perspective. *Haematologica*, **91**, 152.

6. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, and Vardiman JW (2008) *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue*. International Agency for Research On Cancer, WHO, Lyon, France.

7. Quintas-Cardama,A. and Cortes,J.E. (2006) Chronic myeloid leukemia: diagnosis and treatment. *Mayo Clin.Proc.* , **81**, 973-988.

8. Johansson,B., Fioretos,T., and Mitelman,F. (2002) Cytogenetic and molecular genetic evolution of chronic myeloid leukemia. *Acta Haematol.*, **107**, 76-94.

9. Babicka,L., Zemanova,Z., Pavlistova,L., Brezinova,J., Ransdorfova,S., Houskova,L., Moravcova,J., Klamova,H., and Michalova,K. (2006) Complex chromosomal rearrangements in patients with chronic myeloid leukemia. *Cancer Genet.Cytogenet.*, **168**, 22-29.

10. Sokal,J.E., Baccarani,M., Russo,D., and Tura,S. (1988) Staging and prognosis in chronic myelogenous leukemia. *Semin.Hematol.*, **25**, 49-61.

11. Barton,M.K. (2012) Improved long-term outcomes of patients with chronic myelogenous leukemia and a rising prevalence of disease. *CA Cancer J Clin.*, **62**, 349-350.

12. Bisen,A. and Claxton,D.F. (2013) Tyrosine kinase targeted treatment of chronic myelogenous leukemia and other myeloproliferative neoplasms. *Adv.Exp.Med.Biol.*, **779**, 179-196.

13. National Comprehenive Cancer Network. NCCN Clinical Practice Guidelins in Oncology: Chronic Myelogenous Leukemia. http://www.nccn.org/professionals/physician_gls/pdf/cml.pdf. 2014.
Ref Type: Report

14. Gurion,R., Gafter-Gvili,A., Vidal,L., Leader,A., Ram,R., Shacham-Abulafia,A., Paul,M., Ben-Bassat,I., Shpilberg,O., and Raanani,P. (2013) Has the time for first-line treatment with second generation tyrosine kinase inhibitors in patients with chronic myelogenous leukemia already come? Systematic review and meta-analysis. *Haematologica*, **98**, 95-102.

15. Santos,F.P. and Cortes,J. (2012) Dasatinib for the treatment of Philadelphia chromosome-positive leukemias. *Expert.Opin.Pharmacother.*, **13**, 2381-2395.

16. Jabbour,E., Branford,S., Saglio,G., Jones,D., Cortes,J.E., and Kantarjian,H.M. (2011) Practical advice for determining the role of BCR-ABL mutations in guiding tyrosine kinase inhibitor therapy in patients with chronic myeloid leukemia. *Cancer*, **117**, 1800-1811.

17. Mauro,M.J. and Maziarz,R.T. (2006) Stem cell transplantation in patients with chronic myelogenous leukemia: when should it be used? *Mayo Clin.Proc.*, **81**, 404-416.

18. Kantarjian,H.M., Shan,J., Jones,D., O'Brien,S., Rios,M.B., Jabbour,E., and Cortes,J. (2009) Significance of increasing levels of minimal residual disease in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in complete cytogenetic response. *J Clin.Oncol.*, **27**, 3659-3663.

19. Kantarjian,H.M., Talpaz,M., O'Brien,S., Jones,D., Giles,F., Garcia-Manero,G., Faderl,S., Ravandi,F., Rios,M.B., Shan,J., and Cortes,J. (2006) Survival Benefit with Imatinib Mesylate versus Interferon Alpha-Based Regimens in Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia. *Blood*.

20. Shimoni,A., Leiba,M., Schleuning,M., Martineau,G., Renaud,M., Koren-Michowitz,M., Ribakovski,E., le,C.P., Arnold,R., Guilhot,F., and Nagler,A. (2009) Prior treatment with the tyrosine kinase inhibitors dasatinib and nilotinib allows stem cell transplantation (SCT) in a less advanced disease phase and does not increase SCT Toxicity in patients with chronic myelogenous leukemia and philadelphia positive acute lymphoblastic leukemia. *Leukemia*, **23**, 190-194.

21. Simon,W., Segel,G.B., and Lichtman,M.A. (2006) Early allogeneic stem cell transplantation for chronic myelogenous leukemia in the imatinib era: A preliminary assessment. *Blood Cells Mol.Dis.*.

22. Vlaanderen,J., Lan,Q., Kromhout,H., Rothman,N., and Vermeulen,R. (2012) Occupational benzene exposure and the risk of chronic myeloid leukemia: a meta-analysis of cohort studies incorporating study quality dimensions. *Am.J Ind.Med.*, **55**, 779-785.

23. Chap,L. and Nimer,S.D. (1994) Chronic myelogenous leukemia following repeated radiation therapy for histiocytosis X. *Leuk.Lymphoma*, **12**, 315-316.

24. Inskip,P.D., Monson,R.R., Wagoner,J.K., Stovall,M., Davis,F.G., Kleinerman,R.A., and Boice,J.D., Jr. (1990) Leukemia following radiotherapy for uterine bleeding. *Radiat.Res.*, **122**, 107-119.

25. Shimon,I., Kneller,A., and Olchovsky,D. (1995) Chronic myeloid leukaemia following 131I treatment for thyroid carcinoma: a report of two cases and review of the literature. *Clin.Endocrinol.(Oxf)*, **43**, 651-654.

26. Preston,D.L., Kusumi,S., Tomonaga,M., Izumi,S., Ron,E., Kuramoto,A., Kamada,N., Dohy,H., Matsuo,T., and Matsui,T. (1994) Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987 [published erratum appears in Radiat Res 1994 Jul;139(1):129]. *Radiat.Res.*, **137**, S68-S97.

27. Kasim,K., Levallois,P., Abdous,B., Auger,P., and Johnson,K.C. (2005) Lifestyle factors and the risk of adult leukemia in Canada. *Cancer Causes Control*, **16**, 489-500.

28. Ranjan,A., Penninga,E., Jelsig,A.M., Hasselbalch,H.C., and Bjerrum,O.W. (2013) Inheritance of the chronic myeloproliferative neoplasms. A systematic review. *Clin.Genet.*, **83**, 99-107.

29. Lichtman,M.A. (2008) Is there an entity of chemically induced BCR-ABL-positive chronic myelogenous leukemia? *Oncologist.*, **13**, 645-654.

30. Brown,L.M., Gibson,R., Blair,A., Burmeister,L.F., Schuman,L.M., Cantor,K.P., and Fraumeni,J.F., Jr. (1992) Smoking and risk of leukemia. *Am.J.Epidemiol.*, **135**, 763-768.

31. Adami,J., Nyren,O., Bergstrom,R., Ekbom,A., Engholm,G., Englund,A., and Glimelius,B. (1998) Smoking and the risk of leukemia, lymphoma, and multiple myeloma (Sweden). *Cancer Causes Control*, **9**, 49-56.

32. Kinlen,L.J. and Rogot,E. (1988) Leukaemia and smoking habits among United States veterans. *BMJ*, **297**, 657-659.

33. Kabat,G.C., Augustine,A., and Hebert,J.R. (1988) Smoking and adult leukemia: a case-control study. *J.Clin.Epidemiol.*, **41**, 907-914.

34. Sandler,D.P., Shore,D.L., Anderson,J.R., Davey,F.R., Arthur,D., Mayer,R.J., Silver,R.T., Weiss,R.B., Moore,J.O., and Schiffer,C.A. (1993) Cigarette smoking and risk of acute leukemia: associations with morphology and cytogenetic abnormalities in bone marrow. *J Natl Cancer Inst.*, **85**, 1994-2003.

35. Nisse,C., Lorthois,C., Dorp,V., Eloy,E., Haguenoer,J.M., and Fenaux,P. (1995) Exposure to occupational and environmental factors in myelodysplastic syndromes. Preliminary results of a case-control study. *Leukemia*, **9**, 693-699.

36. Mills,P.K., Newell,G.R., Beeson,W.L., Fraser,G.E., and Phillips,R.L. (1990) History of cigarette smoking and risk of leukemia and myeloma: results from the Adventist health study [see comments]. *J Natl Cancer Inst.*, **82**, 1832-1836.

37. Mele,A., Stazi,M.A., Pulsoni,A., Visani,G., Monarca,B., Castelli,G., Rocchi,L., Avvisati,G., and Mandelli,F. (1995) Epidemiology of acute promyelocytic leukemia. *Haematologica*, **80**, 405-408.

38. Kane,E.V., Roman,E., Cartwright,R., Parker,J., and Morgan,G. (1999) Tobacco and the risk of acute leukaemia in adults. *Br J Cancer*, **81**, 1228-1233.

39. Nisse,C., Haguenoer,J.M., Grandbastien,B., Preudhomme,C., Fontaine,B., Brillet,J.M., Lejeune,R., and Fenaux,P. (2001) Occupational and environmental risk factors of the myelodysplastic syndromes in the North of France. *Br J Haematol.*, **112**, 927-935.

40. Mele,A., Szklo,M., Visani,G., Stazi,M.A., Castelli,G., Pasquini,P., and Mandelli,F. (1994) Hair dye use and other risk factors for leukemia and pre-leukemia: a case-control study. Italian Leukemia Study Group. *Am.J.Epidemiol.*, **139**, 609-619.

41. Speer,S.A., Semenza,J.C., Kurosaki,T., and Anton-Culver,H. (2002) Risk factors for acute myeloid leukemia

and multiple myeloma: a combination of GIS and case-control studies. *J Environ Health*, **64**, 9-16.

42. Pasqualetti,P., Festuccia,V., Acitelli,P., Collacciani,A., Giusti,A., and Casale,R. (1997) Tobacco smoking and risk of haematological malignancies in adults: a case-control study. *Br.J.Haematol.*, **97**, 659-662.

43. Linet,M.S., McLaughlin,J.K., Hsing,A.W., Wacholder,S., Co-Chien,H.T., Schuman,L.M., Bjelke,E., and Blot,W.J. (1991) Cigarette smoking and leukemia: results from the Lutheran Brotherhood Cohort Study. *Cancer Causes Control*, **2**, 413-417.

44. Leone,G., Mele,L., Pulsoni,A., Equitani,F., and Pagano,L. (1999) The incidence of secondary leukemias. *Haematologica*, **84**, 937-945.

45. Dann,E.J. and Rowe,J.M. (2001) Biology and therapy of secondary leukaemias. *Best.Pract.Res Clin Haematol.*, **14**, 119-137.

46. Blayney,D.W., Longo,D.L., Young,R.C., Greene,M.H., Hubbard,S.M., Postal,M.G., Duffey,P.L., and DeVita,V.T., Jr. (1987) Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. *N.Engl.J Med*, **316**, 710-714.

47. Boivin,J.F., Hutchison,G.B., Zauber,A.G., Bernstein,L., Davis,F.G., Michel,R.P., Zanke,B., Tan,C.T., Fuller,L.M., Mauch,P., and . (1995) Incidence of second cancers in patients treated for Hodgkin's disease. *J Natl Cancer Inst.*, **87**, 732-741.

48. Schoch,C., Kern,W., Schnittger,S., Hiddemann,W., and Haferlach,T. (2004) Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. *Leukemia*, **18**, 120-125.

49. Kern,W., Haferlach,T., Schnittger,S., Hiddemann,W., and Schoch,C. (2004) Prognosis in therapy-related acute myeloid leukemia and impact of karyotype. *J Clin Oncol*, **22**, 2510-2511.

50. Felix,C.A. (1998) Secondary leukemias induced by topoisomerase-targeted drugs. *Biochim.Biophys.Acta*, **1400**, 233-255.

51. Andersen,M.K., Johansson,B., Larsen,S.O., and Pedersen-Bjergaard,J. (1998) Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. *Haematologica*, **83**, 483-488.

52. Pedersen-Bjergaard,J., Brondum-Nielsen,K., Karle,H., and Johansson,B. (1997) Chemotherapy-related - late occurring - Philadelphia chromosome in AML, ALL and CML. Similar events related to treatment with DNA topoisomerase II inhibitors? *Leukemia*, **11**, 1571-1574.

53. Bacher,U., Kern,W., Schnittger,S., Hiddemann,W., Schoch,C., and Haferlach,T. (2005) Further correlations of morphology according to FAB and WHO classification to cytogenetics in de novo acute myeloid leukemia: a study on 2,235 patients. *Ann.Hematol.*, **84**, 785-791.

54. Klaus,M., Haferlach,T., Schnittger,S., Kern,W., Hiddemann,W., and Schoch,C. (2004) Cytogenetic profile in de novo acute myeloid leukemia with FAB subtypes M0, M1, and M2: a study based on 652 cases analyzed with morphology, cytogenetics, and fluorescence in situ hybridization. *Cancer Genet.Cytogenet.*, **155**, 47-56.

55. Mrozek,K., Heerema,N.A., and Bloomfield,C.D. (2004) Cytogenetics in acute leukemia. *Blood Rev.*, **18**, 115-136.

56. Richardson,S., Zittoun,R., Bastuji-Garin,S., Lasserre,V., Guihenneuc,C., Cadiou,M., Viguie,F., and Laffont-Faust,I. (1992) Occupational risk factors for acute leukaemia: a case-control study. *Int.J.Epidemiol.*, **21**, 1063-1073.

57. Crane,M.M., Strom,S.S., Halabi,S., Berman,E.L., Fueger,J.J., Spitz,M.R., and Keating,M.J. (1996) Correlation between selected environmental exposures and karyotype in acute myelocytic leukemia. *Cancer Epidemiol Biomarkers Prev*, **5**, 639-644.

58. Bennett,J.M. (1995) Secondary acute myeloid leukemia. *Leuk.Res*, **19**, 231-232.

59. Espinos,C., Calpena,E., Martinez-Rubio,D., and Lupo,V. (2012) Autosomal recessive Charcot-Marie-Tooth neuropathy. *Adv.Exp.Med.Biol.*, **724**, 61-75.

60. Saporta,M.A. and Shy,M.E. (2013) Inherited peripheral neuropathies. *Neurol.Clin.*, **31**, 597-619.

61. Tazir,M., Bellatache,M., Nouioua,S., and Vallat,J.M. (2013) Autosomal recessive Charcot-Marie-Tooth disease: from genes to phenotypes. *J Peripher.Nerv.Syst.*, **18**, 113-129.

62. Hill,A.B. (1965) The environment and disease: association or causation. *Proc.Royal Soc.Med.*, **58**, 295-300.

63. Rothman,K.J. and Greenland,S. (2005) Causation and causal inference in epidemiology. *Am J Public Health*, **95 Suppl 1**, S144-S150.

64. Olsen,J. (2003) What characterises a useful concept of causation in epidemiology? *J Epidemiol Community Health*, **57**, 86-88.

65. Parascandola,M. and Weed,D.L. (2001) Causation in epidemiology. *J Epidemiol Community Health*, **55**, 905-912.

66. Lipton,R. and Odegaard,T. (2005) Causal thinking and causal language in epidemiology: it's in the details. *Epidemiol Perspect.Innov.*, **2**, 8.

67. U.S.Department of Health and Human Services,C.f.D.C.a.P.N.C.f.C.D.P.a.H.P.O.o.S.a.H. (2014) *The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General*. U.S. Department of Health and Human Services, Atlanta, Georgia.

68. Advisory Committee to the Surgeon General of the Public Health Service, Washington DC. U.S. Public Health Service, Smoking and health. Publication no.1103. 1964. Washington, DC, U.S.Department of Health,Education and Welfare.
Ref Type: Report

69. Thygesen,L.C., Andersen,G.S., and Andersen,H. (2005) A philosophical analysis of the Hill criteria. *J.Epidemiol.Community Health*, **59**, 512-516.

70. Yuspa,S. and Shields,P.G. (2008) Principles of Carcinogenesis: Chemical. In In DeVita,V.T., Hellman,S., and Rosenberg,S.A. (eds.) *Cancer: Principles and Practice of Oncology*. J.B. Lippincott Co., Philadelphia, PA.

71. Sell,S. (2010) On the stem cell origin of cancer. *Am.J.Pathol.*, **176**, 2584-494.

72. Vineis,P., Schatzkin,A., and Potter,J.D. (2010) Models of carcinogenesis: an overview. *Carcinogenesis*, **31**, 1703-1709.

73. Kulawiec,M., Salk,J.J., Ericson,N.G., Wanagat,J., and Bielas,J.H. (2010) Generation, function, and prognostic utility of somatic mitochondrial DNA mutations in cancer. *Environ.Mol.Mutagen.*, **51**, 427-439.

74. Cabarcas,S.M., Mathews,L.A., and Farrar,W.L. (2011) The cancer stem cell niche--there goes the neighborhood? *Int.J Cancer*, **129**, 2315-2327.

75. Boral,D. and Nie,D. (2012) Cancer stem cells and niche mircoenvironments. *Front Biosci.(Elite.Ed)*, **4**, 2502-2514.

76. Chen,T. (2010) The role of MicroRNA in chemical carcinogenesis. *J.Environ.Sci.Health C.Environ.Carcinog.Ecotoxicol.Rev.*, **28**, 89-124.

77. Taby,R. and Issa,J.P. (2010) Cancer epigenetics. *CA Cancer J.Clin.*, **60**, 376-392.

78. Ushijima,T. and Asada,K. (2010) Aberrant DNA methylation in contrast with mutations. *Cancer Sci.*, **101**, 300-305.

79. Bianchi,N.O. (2010) Mitochondrial genome instability in cancer. *Cytogenet.Genome Res.*, **128**, 66-76.

80. Molchadsky,A., Rivlin,N., Brosh,R., Rotter,V., and Sarig,R. (2010) p53 is balancing development, differentiation and de-differentiation to assure cancer prevention. *Carcinogenesis*, **31**, 1501-1508.

81. Muller-Hubenthal,B., Azemar,M., Lorenzen,D., Huber,M., Freudenberg,M.A., Galanos,C., Unger,C., and Hildenbrand,B. (2009) Tumour Biology: tumour-associated inflammation versus antitumor immunity. *Anticancer Res.*, **29**, 4795-4805.

82. Schetter,A.J., Heegaard,N.H., and Harris,C.C. (2010) Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. *Carcinogenesis*, **31**, 37-49.

83. Compare,D. and Nardone,G. (2011) Contribution of gut microbiota to colonic and extracolonic cancer development. *Dig.Dis.*, **29**, 554-561.

84. Chen,R. and Snyder,M. (2013) Promise of personalized omics to precision medicine. *Wiley.Interdiscip.Rev.Syst.Biol.Med.*, **5**, 73-82.

85. Lynch,S. and Rebbeck,T.R. (2013) Bridging the Gap between Biological, Individual and Macro-Environmental Factors in Cancer: A Multi-Level Approach. *Cancer Epidemiol.Biomarkers Prev.*.

86. Ames,B.N. and Gold,L.S. (2000) Paracelsus to parascience: the environmental cancer distraction. *Mutat.Res.*, **447**, 3-13.

87. Ames,B.N., Shigenaga,M.K., and Gold,L.S. (1993) DNA lesions, inducible DNA repair, and cell division: three key factors in mutagenesis and carcinogenesis. *Environ Health Perspect.*, **101 Suppl 5**, 35-44.

88. Goldman,R. and Shields,P.G. (2003) Food mutagens. *J.Nutr.*, **133 Suppl 3**, 965S-973S.

89. Felton,J.S. and Knize,M.G. (2006) A meat and potato war: implications for cancer etiology. *Carcinogenesis*, **27**, 2367-2370.

90. Jemal,A., Murray,T., Ward,E., Samuels,A., Tiwari,R.C., Ghafoor,A., Feuer,E.J., and Thun,M.J. (2005) Cancer statistics, 2005. *CA Cancer J Clin*, **55**, 10-30.

91. Valent,P. (2012) Low blood counts: immune mediated, idiopathic, or myelodysplasia. *Hematology.Am.Soc.Hematol.Educ.Program.*, **2012**, 485-491.

92. Alberg,A.J., Brock,M.V., and Samet,J.M. (2005) Epidemiology of lung cancer: looking to the future. *J.Clin.Oncol.*, **23**, 3175-3185.

93. Proctor,R.N. (2004) The global smoking epidemic: a history and status report. *Clin Lung Cancer*, **5**, 371-376.

94. Doll,R. and Hill,A.B. (1950) Smoking and carcinoma of the lung: Preliminary report. *Br.Med.J.*, **2**, 739-748.

95. Wynder,E.L. and Graham,E.A. (1950) Tobacco smoking as a possible etiologic factor in bronchogenic carcinoma. *J.A.M.A.*, **143**, 329-336.

96. PUblic Health Service. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. PHS publication No. 1103. 1964.
Ref Type: Report

97. Barbone,F., Bovenzi,M., Cavallieri,F., and Stanta,G. (1997) Cigarette smoking and histologic type of lung cancer in men. *Chest*, **112**, 1474-1479.

98. Bjartveit,K. and Tverdal,A. (2005) Health consequences of smoking 1-4 cigarettes per day. *Tob Control*, **14**, 315-320.

99. Parkin,D.M., Pisani,P., and Ferlay,J. (1999) Global cancer statistics. *CA Cancer J Clin*, **49**, 33-64, 2.

100. Lofroth,G. and Zebuhr,Y. (1992) Polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) in mainstream and sidestream cigarette smoke. *Bull.Environ.Contam Toxicol.*, **48**, 789-794.

101. Kasai,A., Hiramatsu,N., Hayakawa,K., Yao,J., Maeda,S., and Kitamura,M. (2006) High levels of dioxin-like potential in cigarette smoke evidenced by in vitro and in vivo biosensing. *Cancer Res.*, **66**, 7143-7150.

102. Fowles,J. and Dybing,E. (2003) Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tob Control*, **12**, 424-430.

103. Muto,H. and Takizawa,Y. (1989) Dioxins in cigarette smoke. *Arch.Environ.Health*, **44**, 171-174.

104. Flanders,W.D., Lally,C.A., Zhu,B.P., Henley,S.J., and Thun,M.J. (2003) Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption: results from Cancer Prevention Study II. *Cancer Res*, **63**, 6556-6562.

105. Knoke,J.D., Shanks,T.G., Vaughn,J.W., Thun,M.J., and Burns,D.M. (2004) Lung cancer mortality is related to age in addition to duration and intensity of cigarette smoking: an analysis of CPS-I data. *Cancer Epidemiol Biomarkers Prev*, **13**, 949-957.

106. Hegmann,K.T., Fraser,A.M., Keaney,R.P., Moser,S.E., Nilasena,D.S., Sedlars,M., Higham-Gren,L., and Lyon,J.L. (1993) The effect of age at smoking initiation on lung cancer risk [see comments]. *Epidemiology*, **4**, 444-448.

107. Benhamou,S., Benhamou,E., Auquier,A., and Flamant,R. (1994) Differential effects of tar content, type of tobacco and use of a filter on lung cancer risk in male cigarette smokers. *Int.J Epidemiol*, **23**, 437-443.

108. Khuder,S.A., Dayal,H.H., Mutgi,A.B., Willey,J.C., and Dayal,G. (1998) Effect of cigarette smoking on major histological types of lung cancer in men [see comments]. *Lung Cancer*, **22**, 15-21.

109. Zang,E.A. and Wynder,E.L. (1992) Cumulative tar exposure. A new index for estimating lung cancer risk among cigarette smokers. *Cancer*, **70**, 69-76.

110. Anthonisen,N.R., Skeans,M.A., Wise,R.A., Manfreda,J., Kanner,R.E., and Connett,J.E. (2005) The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann.Intern.Med.*, **142**, 233-239.

111. Stellman,S.D. and Garfinkel,L. (1989) Lung cancer risk is proportional to cigarette tar yield: evidence from a prospective study. *Prev.Med*, **18**, 518-525.

112. Garfinkel,L. and Stellman,S.D. (1988) Smoking and lung cancer in women: findings in a prospective study. *Cancer Res*, **48**, 6951-6955.

113. McLaughlin,J.K., Hrubec,Z., Blot,W.J., and Fraumeni,J.F., Jr. (1995) Smoking and cancer mortality among U.S. veterans: a 26-year follow-up. *Int.J Cancer*, **60**, 190-193.

114. Akiba,S. and Hirayama,T. (1990) Cigarette smoking and cancer mortality risk in Japanese men and women--results from reanalysis of the six-prefecture cohort study data. *Environ Health Perspect.*, **87**, 19-26.

115. Hammond,E.C. and Horn,D. (1988) Smoking and death rates--report on forty-four months of follow-up of 187,783 men. By E. Cuyler Hammond and Daniel Horn, 1958 [classical article]. *CA Cancer J Clin.*, **38**, 28-58.

116. International Agency for Research on Cancer (2004) Tobacco smoke and involuntary smoking. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. IARC, Lyon, France.

117. Weir,J.M. and Dunn,J.E., Jr. (1970) Smoking and mortality: a prospective study. *Cancer*, **25**, 105-112.

118. Kuller,L.H., Ockene,J.K., Meilahn,E., Wentworth,D.N., Svendsen,K.H., and Neaton,J.D. (1991) Cigarette smoking and mortality. MRFIT Research Group. *Prev.Med*, **20**, 638-654.

119. Potter,J.D., Sellers,T.A., Folsom,A.R., and McGovern,P.G. (1992) Alcohol, beer, and lung cancer in postmenopausal women. The Iowa Women's Health Study. *Ann.Epidemiol*, **2**, 587-595.

120. Tverdal,A., Thelle,D., Stensvold,I., Leren,P., and Bjartveit,K. (1993) Mortality in relation to smoking history: 13 years' follow-up of 68,000 Norwegian men and women 35-49 years. *J Clin Epidemiol*, **46**, 475-487.

121. Thun,M.J., Carter,B.D., Feskanich,D., Freedman,N.D., Prentice,R., Lopez,A.D., Hartge,P., and Gapstur,S.M. (2013) 50-year trends in smoking-related mortality in the United States. *N.Engl.J Med.*, **368**, 351-364.

122. Harris,J.E., Thun,M.J., Mondul,A.M., and Calle,E.E. (2004) Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982-8. *BMJ*, **328**, 72-76.

123. Benhamou,E., Benhamou,S., Auquier,A., and Flamant,R. (1989) Changes in patterns of cigarette smoking and lung cancer risk: results of a case-control study. *Br J Cancer*, **60**, 601-604.

124. Khuder,S.A., Dayal,H.H., Mutgi,A.B., Willey,J.C., and Dayal,G. (1998) Effect of cigarette smoking on major histological types of lung cancer in men. *Lung Cancer*, **22**, 15-21.

125. Wynder,E.L. and Stellman,S.D. (1979) Impact of long-term filter cigarette usage on lung and larynx cancer risk: a case-control study. *J Natl Cancer Inst.*, **62**, 471-477.

126. Augustine,A., Harris,R.E., and Wynder,E.L. (1989) Compensation as a risk factor for lung cancer in smokers who switch from nonfilter to filter cigarettes. *Am J Public Health*, **79**, 188-191.

127. Rimington,J. (1981) The effect of filters on the incidence of lung cancer in cigarette smokers. *Environ.Res*, **24**, 162-166.

128. Pathak,D.R., Samet,J.M., Humble,C.G., and Skipper,B.J. (1986) Determinants of lung cancer risk in cigarette smokers in New Mexico. *J Natl Cancer Inst.*, **76**, 597-604.

129. Lubin,J.H., Blot,W.J., Berrino,F., Flamant,R., Gillis,C.R., Kunze,M., Schmahl,D., and Visco,G. (1984) Patterns of lung cancer risk according to type of cigarette smoked. *Int.J Cancer*, **33**, 569-576.

130. Wilcox,H.B., Schoenberg,J.B., Mason,T.J., Bill,J.S., and Stemhagen,A. (1988) Smoking and lung cancer: risk as a function of cigarette tar content. *Prev.Med*, **17**, 263-272.

131. Tang,J.L., Morris,J.K., Wald,N.J., Hole,D., Shipley,M., and Tunstall-Pedoe,H. (1995) Mortality in relation to tar yield of cigarettes: a prospective study of four cohorts. *BMJ*, **311**, 1530-1533.

132. Sidney,S., Tekawa,I.S., and Friedman,G.D. (1993) A prospective study of cigarette tar yield and lung cancer. *Cancer Causes.Control.*, **4**, 3-10.

133. Stellman,S.D., Muscat,J.E., Hoffmann,D., and Wynder,E.L. (1997) Impact of filter cigarette smoking on lung cancer histology. *Prev.Med*, **26**, 451-456.

134. Lubin,J.H. and Blot,W.J. (1984) Assessment of lung cancer risk factors by histologic category. *J Natl.Cancer Inst.*, **73**, 383-389.

135. Godtfredsen,N., Prescott,E., and Osler,M. (2005) Effect of smoking reduction on lung cancer risk. *JAMA*, **294**, 1505-1510.

136. Brownson,R.C., Alavanja,M.C., Caporaso,N., Simoes,E.J., and Chang,J.C. (1998) Epidemiology and prevention of lung cancer in nonsmokers. *Epidemiol.Rev.*, **20**, 218-236.

137. Zeise, L., Dunn, A., Haroun, L., Ting, D., Windham, G., Golub, M., Waller, K., Lipsett, M., Shusterman, D., Mann, J., and Wu, A. Health Effects of Exposure to Environmental Tobacco Smoke. Office of Health and Environmental Health Hazard Assessment. 1997. California, Environmental Protection Agency.
Ref Type: Report

138. Brownson,R.C., Eriksen,M.P., Davis,R.M., and Warner,K.E. (1997) Environmental tobacco smoke: health effects and policies to reduce exposure. *Annu.Rev.Public Health*, **18**, 163-185.

139. Sunyer,J., Munoz,A., Peng,Y., Margolick,J., Chmiel,J.S., Oishi,J., Kingsley,L., and Samet,J.M. (1996) Longitudinal relation between smoking and white blood cells. *Am J Epidemiol*, **144**, 734-741.

140. U.S.Department of Health and Human Services National Cancer Institute. The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Number 7, 238-247. 1996. Bethesda, MD, U.S. Department of Health and Human Services, NIH. Smoking and Tobacco Control Monograph.
Ref Type: Report

141. Fontham,E.T.H., Correa,P., Wu-Williams,A., Reynolds,P., Greenberg,R.S., Buffler,P.A., Chen,V.W., Boyd,P., Alterman,T., Austin,D.F., Liff,J., and Greenberg,S.D. (1991) Lung cancer in non-smoking women: a multicenter case-control study. *CEBP*, **1**, 35-43.

142. Janerich,D.T., Thompson,W.D., Varela,L.R., Greenwald,P., Chorost,S., Tucci,C., Zaman,M.B., Melamed,M.R., Kiely,M., and McKneally,M.F. (1990) Lung cancer and exposure to tobacco smoke in the household. *N.Engl.J.Med.*, **323**, 632-636.

143. Stockwell,H.G., Goldman,A.L., Lyman,G.H., Noss,C.I., Armstrong,A.W., Pinkham,P.A., Candelora,E.C., and Brusa,M.R. (1992) Environmental tobacco smoke and lung cancer risk in nonsmoking women [see comments]. *J Natl.Cancer Inst.*, **84**, 1417-1422.

144. Tweedie,R.L. and Mengersen,K.L. (1992) Lung cancer and passive smoking: reconciling the biochemical and epidemiological approaches. *Br.J Cancer*, **66**, 700-705.

145. Darby,S.C. and Pike,M.C. (1988) Lung cancer and passive smoking: predicted effects from a mathematical model for cigarette smoking and lung cancer [see comments]. *Br J Cancer*, **58**, 825-831.

146. Lee,P.N. (1998) Difficulties in assessing the relationship between passive smoking and lung cancer. *Stat.Methods Med.Res.*, **7**, 137-163.

147. Amoruso,M.A., Gamble,J.F., McKee,R.H., Rohde,A.M., and Jaques,A. (2008) Review of the toxicology of mineral spirits. *Int.J.Toxicol.*, **27**, 97-165.

148. Williams,P.R., Panko,J.M., Unice,K., Brown,J.L., and Paustenbach,D.J. (2008) Occupational exposures associated with petroleum-derived products containing trace levels of benzene. *J.Occup.Environ.Hyg.*, **5**, 565-574.

149. Farmer,P.B., Kaur,B., Roach,J., Levy,L., Consonni,D., Bertazzi,P.A., Pesatori,A., Fustinoni,S., Buratti,M., Bonzini,M., Colombi,A., Popov,T., Cavallo,D., Desideri,A., Valerio,F., Pala,M., Bolognesi,C., and Merlo,F. (2005) The use of S-phenylmercapturic acid as a biomarker in molecular epidemiology studies of benzene. *Chem.Biol.Interact.*, **153-154**, 97-102.

150. US Department of Health and Human Services, Agency for Toxic Substances Disease Registry. Toxicological Profile For Stoddard Solvent. 1995. Atlanta, Georgia.
Ref Type: Report

151. Travis,R.C., Crowe,F.L., Allen,N.E., Appleby,P.N., Roddam,A.W., Tjonneland,A., Olsen,A., Linseisen,J., Kaaks,R., Boeing,H., Kroger,J., Trichopoulou,A., Dilis,V., Trichopoulos,D., Vineis,P., Palli,D., Tumino,R., Sieri,S., Bueno-de-Mesquita,H.B., van Duijnhoven,F.J., Chirlaque,M.D., Barricarte,A., Larranaga,N., Gonzalez,C.A., Arguelles,M.V., Sanchez,M.J., Stattin,P., Hallmans,G., Khaw,K.T., Bingham,S., Rinaldi,S., Slimani,N., Jenab,M., Riboli,E., and Key,T.J. (2009) Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am.J Epidemiol*, **169**, 1223-1232.

152. National Toxicology Program (2004) NTP technical report on the toxicology and carcinogenesis studies of Stoddard Solvent IIC (Cas No. 64742-88-7) in F344/N rats and B6C3F1 mice (inhalation studies) (Full report available at http://ntp.niehs.nih.gov/?objectid=070B6237-90A2-64B7-51F51385A1F3869F). *Natl.Toxicol.Program.Tech.Rep.Ser.*,1-274.

153. Plisko MJ and Spencer JW (2008) Evaluation of a mathematical model for estimating solvent exppsiires in the workplace. *J.Chem.Health Safety*, **doi:I0.1016/j.jchas.2007.11.002**, 1-8.

154. Nicas,M., Plisko,M.J., and Spencer,J.W. (2006) Estimating benzene exposure at a solvent parts washer. *J.Occup.Environ.Hyg.*, **3**, 284-291.

155. Fedoruk,M.J., Bronstein,R., and Kerger,B.D. (2003) Benzene exposure assessment for use of a mineral spirits-based degreaser. *Appl.Occup.Environ.Hyg.*, **18**, 764-771.

156. Vlaanderen,J., Lan,Q., Kromhout,H., Rothmann,N., and Vermeulen,R. (2010) Occupational Benzene Exposure and the Risk of Lymphoma Subtypes: a Meta-Analysis of Cohort Studies Incorporating Three Study Quality Dimensions. *Environ.Health Perspect.*.

157. Natelson,E.A. (2007) Benzene-induced acute myeloid leukemia: a clinician's perspective. *Am.J Hematol.*, **82**, 826-830.

158. Khalade,A., Jaakkola,M.S., Pukkala,E., and Jaakkola,J.J. (2010) Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environ.Health*, **9**, 31.

159. Galbraith,D., Gross,S.A., and Paustenbach,D. (2010) Benzene and human health: A historical review and appraisal of associations with various diseases. *Crit Rev.Toxicol.*, **40 Suppl 2**, 1-46.

160. Schnatter,A.R., Glass,D.C., Tang,G., Irons,R.D., and Rushton,L. (2012) Myelodysplastic Syndrome and Benzene Exposure Among Petroleum Workers: An International Pooled Analysis. *J.Natl.Cancer Inst.*.

161. Lewis,S.J., Bell,G.M., Cordingley,N., Pearlman,E.D., and Rushton,L. (1997) Retrospective estimation of exposure to benzene in a leukaemia case- control study of petroleum marketing and distribution workers in the United Kingdom. *Occup.Environ Med*, **54**, 167-175.

162. Silver,S.R., Rinsky,R.A., Cooper,S.P., Hornung,R.W., and Lai,D. (2002) Effect of follow-up time on risk estimates: a longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort. *Am J Ind.Med*, **42**, 481-489.

163. Rinsky,R.A., Hornung,R.W., Silver,S.R., and Tseng,C.Y. (2002) Benzene exposure and hematopoietic mortality: A long-term epidemiologic risk assessment. *Am J Ind.Med*, **42**, 474-480.

164. Hayes,R.B., Yin,S.N., Dosemeci,M., Li,G.L., Wacholder,S., Travis,L.B., Li,C.Y., Rothman,N., Hoover,R.N., and Linet,M.S. (1997) Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group [see comments]. *J Natl Cancer Inst.*, **89**, 1065-1071.

165. Vlaanderen,J., Portengen,L., Rothman,N., Lan,Q., Kromhout,H., and Vermeulen,R. (2010) Flexible meta-regression to assess the shape of the benzene-leukemia exposure-response curve. *Environ.Health Perspect.*, **118**, 526-532.

166. Rushton,L., Schnatter,A.R., Tang,G., and Glass,D.C. (2013) Acute myeloid and chronic lymphoid leukaemias and exposure to low-level benzene among petroleum workers. *Br.J Cancer*.

167. Capleton,A.C. and Levy,L.S. (2005) An overview of occupational benzene exposures and occupational exposure limits in Europe and North America. *Chem.Biol.Interact.*, **153-154**, 43-53.

168. Weisel,C.P. (2010) Benzene exposure: an overview of monitoring methods and their findings. *Chem.Biol.Interact.*, **184**, 58-66.

169. Wallace,L. (1996) Environmental exposure to benzene: an update. *Environ.Health Perspect.*, **104 Suppl 6**, 1129-1136.

170. Pyatt,D. (2004) Benzene and hematopoietic malignancies. *Clin.Occup.Environ.Med.*, **4**, 529-555.

171. Johnson,E.S., Langard,S., and Lin,Y.S. (2007) A critique of benzene exposure in the general population. *Sci Total Environ.*, **374**, 183-198.

172. Chen,M.L., Chen,S.H., Guo,B.R., and Mao,I.F. (2002) Relationship between environmental exposure to toluene, xylene and ethylbenzene and the expired breath concentrations for gasoline service workers. *J Environ Monit.*, **4**, 562-566.

173. Periago,J.F. and Prado,C. (2005) Evolution of occupational exposure to environmental levels of aromatic hydrocarbons in service stations. *Ann.Occup Hyg.*, **49**, 233-240.

174. American Conference of Governmental Hygeinists (2001) Benzene: Biological Exposure Index. *Documentation of Threshold Limit Values and Biological Exposure Indices*.

175. Fustinoni,S., Campo,L., Mercadante,R., and Manini,P. (2010) Methodological issues in the biological monitoring of urinary benzene and S-phenylmercapturic acid at low exposure levels. *J Chromatogr.B Analyt.Technol.Biomed.Life Sci.*, **878**, 2534-2540.

176. Fracasso,M.E., Doria,D., Bartolucci,G.B., Carrieri,M., Lovreglio,P., Ballini,A., Soleo,L., Tranfo,G., and Manno,M. (2010) Low air levels of benzene: correlation between biomarkers of exposure and genotoxic effects. *Toxicol.Lett.*, **192**, 22-28.

177. Carrieri,M., Bonfiglio,E., Scapellato,M.L., Macca,I., Tranfo,G., Faranda,P., Paci,E., and Bartolucci,G.B.

(2006) Comparison of exposure assessment methods in occupational exposure to benzene in gasoline filling-station attendants. *Toxicol.Lett.*, **162**, 146-152.

178. Navasumrit,P., Chanvaivit,S., Intarasunanont,P., Arayasiri,M., Lauhareungpanya,N., Parnlob,V., Settachan,D., and Ruchirawat,M. (2005) Environmental and occupational exposure to benzene in Thailand. *Chem.Biol.Interact.*, **153-154**, 75-83.

179. Fustinoni,S., Buratti,M., Campo,L., Colombi,A., Consonni,D., Pesatori,A.C., Bonzini,M., Farmer,P., Garte,S., Valerio,F., Merlo,D.F., and Bertazzi,P.A. (2005) Urinary t,t-muconic acid, S-phenylmercapturic acid and benzene as biomarkers of low benzene exposure. *Chem.Biol.Interact.*, **153-154**, 253-256.

180. Manini,P., De,P.G., Andreoli,R., Mozzoni,P., Poli,D., Goldoni,M., Petyx,M., Apostoli,P., and Mutti,A. (2010) Occupational exposure to low levels of benzene: Biomarkers of exposure and nucleic acid oxidation and their modulation by polymorphic xenobiotic metabolizing enzymes. *Toxicol.Lett.*, **193**, 229-235.

181. Rekhadevi,P.V., Mahboob,M., Rahman,M.F., and Grover,P. (2010) Determination of genetic damage and urinary metabolites in fuel filling station attendants. *Environ.Mol.Mutagen.*.

182. Tunsaringkarn,T., Suwansaksri,J., Soogarun,S., Siriwong,W., Rungsiyothin,A., Zapuang,K., and Robson,M. (2011) Genotoxic monitoring and benzene exposure assessment of gasoline station workers in metropolitan Bangkok: sister chromatid exchange (SCE) and urinary trans, trans-muconic acid (t,t-MA). *Asian Pac.J Cancer Prev.*, **12**, 223-227.

183. Popp,W., Rauscher,D., Muller,G., Angerer,J., and Norpoth,K. (1994) Concentrations of benzene in blood and S-phenylmercapturic and t,t-muconic acid in urine in car mechanics. *Int.Arch.Occup Environ.Health*, **66**, 1-6.

184. Tunsaringkarn,T., Soogarun,S., and Palasuwan,A. (2013) Occupational exposure to benzene and changes in hematological parameters and urinary trans, trans-muconic acid. *Int.J Occup Environ.Med.*, **4**, 45-49.

185. Schnatter,A.R., Rosamilia,K., and Wojcik,N.C. (2005) Review of the literature on benzene exposure and leukemia subtypes. *Chem.Biol.Interact.*, **153-154**, 9-21.

186. Saberi,H.F., Christopher,Y., Peeters,P., Romieu,I., Xun,W., Riboli,E., Raaschou-Nielsen,O., Tjonneland,A., Becker,N., Nieters,A., Trichopoulou,A., Bamia,C., Orfanos,P., Oddone,E., Lujan-Barroso,L., Dorronsoro,M., Navarro,C., Barricarte,A., Molina-Montes,E., Wareham,N., Vineis,P., and Vermeulen,R. (2013) Occupation and risk of lymphoid and myeloid leukaemia in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Occup Environ.Med.*, **70**, 464-470.

187. Bjork,J., Albin,M., Welinder,H., Tinnerberg,H., Mauritzson,N., Kauppinen,T., Stromberg,U., Johansson,B., Billstrom,R., Mikoczy,Z., Ahlgren,T., Nilsson,P.G., Mitelman,F., and Hagmar,L. (2001) Are occupational, hobby, or lifestyle exposures associated with Philadelphia chromosome positive chronic myeloid leukaemia? *Occup Environ Med*, **58**, 722-727.

188. Hayes,R.B., Yin,S., Rothman,N., Dosemeci,M., Li,G., Travis,L.T., Smith,M.T., and Linet,M.S. (2000) Benzene and lymphohematopoietic malignancies in China. *J Toxicol Environ Health A*, **61**, 419-432.

189. Travis,L.B., Li,C.Y., Zhang,Z.N., Li,D.G., Yin,S.N., Chow,W.H., Li,G.L., Dosemeci,M., Blot,W., Fraumeni,J.F., Jr., and . (1994) Hematopoietic malignancies and related disorders among benzene-exposed workers

in China. *Leuk.Lymphoma*, **14**, 91-102.

190. Yin,S.N., Hayes,R.B., Linet,M.S., Li,G.L., Dosemeci,M., Travis,L.B., Li,C.Y., Zhang,Z.N., Li,D.G., Chow,W.H., Wacholder,S., Wang,Y.Z., Jiang,Z.L., Dai,T.R., Zhang,W.Y., Chao,X.J., Ye,P.Z., Kou,Q.R., Zhang,X.C., Lin,X.F., Meng,J.F., Ding,C.Y., Zho,J.S., and Blot,W.J. (1996) A cohort study of cancer among benzene-exposed workers in China: overall results. *Am.J.Ind.Med.*, **29**, 227-235.

191. Aksoy,M. and Erdem,S. (1978) Followup study on the mortality and the development of leukemia in 44 pancytopenic patients with chronic exposure to benzene. *Blood*, **52**, 285-292.

192. Aksoy,M. (1985) Malignancies due to occupational exposure to benzene. *Am J Ind.Med*, **7**, 395-402.

193. Aksoy,M., Erdem,S., and Dincol,G. (1976) Types of leukemia in chronic benzene poisoning. A study in thirty-four patients. *Acta Haematol.*, **55**, 65-72.

194. Ke,L. and Shunzhang,Y. (1999) Economic status and occupational correlates of stomach cancer in the rubber industry. *Int.J Occup Med Environ Health*, **12**, 345-352.

195. Norseth,T., Andersen,A., and Giltvedt,J. (1983) Cancer incidence in the rubber industry in Norway. *Scand J Work Environ Health*, **9 Suppl 2**, 69-71.

196. Vigliani,E.C. (1976) Leukemia associated with benzene exposure. *Ann.N.Y.Acad.Sci.*, **271**, 143-151.

197. Glass,D.C., Gray,C.N., Jolley,D.J., Gibbons,C., Sim,M.R., Fritschi,L., Adams,G.G., Bisby,J.A., and Manuell,R. (2003) Leukemia risk associated with low-level benzene exposure. *Epidemiology*, **14**, 569-577.

198. Rushton,L. and Romaniuk,H. (1997) A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom [see comments]. *Occup.Environ Med*, **54**, 152-166.

199. Gun,R.T., Pratt,N.L., Griffith,E.C., Adams,G.G., Bisby,J.A., and Robinson,K.L. (2004) Update of a prospective study of mortality and cancer incidence in the Australian petroleum industry. *Occup Environ Med*, **61**, 150-156.

200. Lewis,R.J., Schnatter,A.R., Katz,A.M., Thompson,F.S., Murray,N., Jorgensen,G., and Theriault,G. (2000) Updated mortality among diverse operating segments of a petroleum company. *Occup Environ Med*, **57**, 595-604.

201. Divine,B.J., Hartman,C.M., and Wendt,J.K. (1999) Update of the Texaco mortality study 1947-93: Part II. Analyses of specific causes of death for white men employed in refining, research, and petrochemicals [see comments]. *Occup.Environ Med*, **56**, 174-180.

202. Wongsrichanalai,C., Delzell,E., and Cole,P. (1989) Mortality from leukemia and other diseases among workers at a petroleum refinery. *J.Occup.Med*, **31**, 106-111.

203. Tsai,S.P., Ahmed,F.S., Wendt,J.K., Foster,D.E., Donnelly,R.P., and Strawmyer,T.R. (2007) A 56-year mortality follow-up of Texas petroleum refinery and chemical employees, 1948-2003. *J Occup Environ.Med.*, **49**, 557-567.

204. Tsai,S.P., Chen,V.W., Fox,E.E., Wendt,J.K., Cheng,W., X, Foster,D.E., and Fraser,A.E. (2004) Cancer incidence among refinery and petrochemical employees in Louisiana, 1983-1999. *Ann.Epidemiol.*, **14**, 722-730.

205. Tsai,S.P., Wendt,J.K., Cardarelli,K.M., and Fraser,A.E. (2003) A mortality and morbidity study of refinery and petrochemical employees in Louisiana. *Occup Environ.Med.*, **60**, 627-633.

206. Tsai,S.P. and Wendt,J.K. (2001) Health findings from a mortality and morbidity surveillance of refinery employees. *Ann.Epidemiol.*, **11**, 466-476.

207. Tsai,S.P., Bennett,J.M., Salesman,C.N., Ryan,T.E., Gilstrap,E.L., and Ross,C.E. (1998) Medical surveillance for hematological disorders among active and retired oil refinery workers. *J Occup Environ.Med.*, **40**, 475-480.

208. Schnatter,A.R., Katz,A.M., Nicolich,M.J., and Theriault,G. (1993) A retrospective mortality study among Canadian petroleum marketing and distribution workers. *Environ Health Perspect.*, **101 Suppl 6**, 85-99.

209. Bloemen,L.J., Youk,A., Bradley,T.D., Bodner,K.M., and Marsh,G. (2004) Lymphohaematopoietic cancer risk among chemical workers exposed to benzene. *Occup.Environ.Med.*, **61**, 270-274.

210. Guenel,P., Imbernon,E., Chevalier,A., Crinquand-Calastreng,A., and Goldberg,M. (2002) Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers. *Am J Ind.Med*, **42**, 87-97.

211. Massoudi,B.L., Talbott,E.O., Day,R.D., Swerdlow,S.H., Marsh,G.M., and Kuller,L.H. (1997) A case-control study of hematopoietic and lymphoid neoplasms: the role of work in the chemical industry [see comments]. *Am.J Ind.Med*, **31**, 21-27.

212. Ireland,B., Collins,J.J., Buckley,C.F., and Riordan,S.G. (1997) Cancer mortality among workers with benzene exposure. *Epidemiology*, **8**, 318-320.

213. Collins,J.J., Ireland,B., Buckley,C.F., and Shepperly,D. (2003) Lymphohaematopoeitic cancer mortality among workers with benzene exposure. *Occup Environ Med*, **60**, 676-679.

214. Bond,G.G., McLaren,E.A., Baldwin,C.L., and Cook,R.R. (1986) An update of mortality among chemical workers exposed to benzene. *Br.J Ind.Med*, **43**, 685-691.

215. Aronson,K.J., Howe,G.R., Carpenter,M., and Fair,M.E. (1999) Surveillance of potential associations between occupations and causes of death in Canada, 1965-91. *Occup.Environ.Med.*, **56**, 265-269.

216. Adegoke,O.J., Blair,A., Shu,X.O., Sanderson,M., Jin,F., Dosemeci,M., Addy,C.L., and Zheng,W. (2003) Occupational history and exposure and the risk of adult leukemia in Shanghai. *Ann.Epidemiol*, **13**, 485-494.

217. Lynge,E., Andersen,A., Nilsson,R., Barlow,L., Pukkala,E., Nordlinder,R., Boffetta,P., Grandjean,P., Heikkila,P., Horte,L.G., Jakobsson,R., Lundberg,I., Moen,B., Partanen,T., and Riise,T. (1997) Risk of cancer and exposure to gasoline vapors. *Am.J.Epidemiol.*, **145**, 449-458.

218. Pukkala,E., Martinsen,J.I., Lynge,E., Gunnarsdottir,H.K., Sparen,P., Tryggvadottir,L., Weiderpass,E., and Kjaerheim,K. (2009) Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol.*, **48**, 646-790.

219. Kaufman,D.W., Anderson,T.E., and Issaragrisil,S. (2009) Risk factors for leukemia in Thailand. *Ann.Hematol.*, **88**, 1079-1088.

220. Troy,J.D., Hartge,P., Weissfeld,J.L., Oken,M.M., Colditz,G.A., Mechanic,L.E., and Morton,L.M. (2010) Associations between anthropometry, cigarette smoking, alcohol consumption, and non-Hodgkin lymphoma in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Am.J.Epidemiol.*, **171**, 1270-1281.

221. Wong,O. and Raabe,G.K. (1995) Cell-type-specific leukemia analyses in a combined cohort of more than 208,000 petroleum workers in the United States and the United Kingdom, 1937-1989. *Regul.Toxicol.Pharmacol.*, **21**, 307-321.

222. Mehlman,M.A. (2006) Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industries. Part XXX: Causal relationship between chronic myelogenous leukemia and benzene-containing solvents. *Ann.N.Y.Acad.Sci.*, **1076**, 110-119.